TARGET-FLOW INSPIRATORY MUSCLE TRAINING AND PULMONARY REHABILITATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

P.N.R. DEKHUIJZEN

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Aan Bep, Pauline en Daniël

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION AND AIMS OF THE STUDY

1-1. GENERAL INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disorder characterized by chronic expiratory airflow limitation, which shows only partial reversibility in spite of continuous medication (1).

Besides the expiratory flow limitation, there may be other pulmonary functional disorders such as a reduced diffusion capacity, an increased dead space/tidal volume ratio, a ventilation-perfusion mismatch, or changes in the elasticity of the lung tissue. All these disorders can contribute to the sensation of dyspnea at exercise. Moreover, to realize an adequate ventilation, an increased work of breathing is necessary, which has to be performed by the respiratory muscle pump. The major part of the work of breathing is performed by the inspiratory muscles, especially the diaphragm and the intercostal muscles. During exercise the work load of these muscles, which are frequently weak in COPD patients (2), is increased. Fatigue of these muscles may then develop and may be one of the limiting factors of the exercise capacity of these patients (3).

Shortness of breath limits patients' activities, leading to a vicious circle of increasing inactivity. This may result in a further decrease of physical fitness and an increase of the fatigability of the inspiratory muscles.

Physical exercise as well as specific inspiratory muscle training have been applied to patients with COPD in order to improve the strength and endurance of the inspiratory muscles and the exercise capacity (4-13). The results are conflicting. Some studies showed that the general exercise capacity had improved after inspiratory muscle training (5,6,10), but this was not the case in other investigations (7,9,11,12).

Most studies did not select COPD patients on the basis of the characteristics of the pulmonary functional disorders, which contributed to the exercise limitation. So it is possible that inspiratory muscle training was applied to patients in whom the performance of the inspiratory muscles was not an important limiting factor of the exercise capacity. Another point of

discussion is whether the inspiratory muscles were adequately trained in most of the studies (4,6,7,9,11,12). Moreover, the number of patients was small and the duration of the training period was short, without a follow-up period in any of these studies.
It is therefore not clear whether all COPD patients, or only certain subgroups, will benefit from standardized inspiratory muscle training, in terms of an increase in performance of the inspiratory muscles and in exercise capacity. What the long-term effects of inspiratory muscle training are, has not yet been studied, either.

1-2. AIMS OF THE STUDY

In this thesis the effects of pulmonary rehabilitation and inspiratory muscle training were studied in COPD patients with a ventilatory limitation of their exercise capacity, i.e. a normal arterial PCO_2 at rest that increases during exercise. Patients with a limitation of the diffusion capacity during exercise were excluded. Twenty patients participated in a pulmonary rehabilitation program. Another twenty patients underwent an inspiratory muscle training program, in which a target-flow was defined as well as the duration of the inspiration and expiration. Pulmonary rehabilitation combined with inspiratory muscle training was applied to a third group of twenty patients.
In chapter 2 of this thesis, the limitations of the functional capacity will be described, with the emphasis on the function and the fatigability of the inspiratory muscles.
The aims of the investigations presented in this study are:
- To measure the effects of target-flow inspiratory muscle training on the breathing pattern and metabolic parameters in COPD patients with a ventilatory limitation during exercise (Chapter 3);
- To investigate if additional target-flow inspiratory muscle training has an additional effect during a general pulmonary rehabilitation program in COPD patients with a ventilatory

limitation on the strength and endurance of the inspiratory muscles and the physical exercise capacity (Chapter 4);

- To compare the effects of an (isolated) inspiratory muscle training program at home with a supervised inspiratory muscle training program during pulmonary rehabilitation (Chapter 5);
- To assess the long-term effects of pulmonary rehabilitation and target-flow inspiratory muscle training during a one-year follow-up period on the performance of the inspiratory muscles and on the physical exercise capacity (Chapter 6);
- And to evaluate the acute and long-term effects of pulmonary rehabilitation and inspiratory muscle training on psychological parameters in these patients (Chapter 7).

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1-4. LIST OF ABBREVIATIONS

COPD	chronic obstructive pulmonary disease
$D(A-a)O_2$	alveolar-arterial oxygen difference
EMG	electromyogram
F_c	centroid (median) frequency of the EMG power spectrum
FEV_1	forced expiratory volume in 1 second
FRC	functional residual capacity
HR	heart rate
HR_{max}	heart rate at maximal exercise
IMT	inspiratory muscle training
IVC	inspiratory vital capacity
K_{CO}	diffusion capacity of the lung for carbon monoxide
MVV	maximal voluntary ventilation
PaO_2	partial pressure of oxygen in the arterial blood
$PaCO_2$	partial pressure of carbon dioxide in the arterial blood
Pdi	transdiaphragmatic pressure
Pdi_{max}	maximal transdiaphragmatic pressure
PI	inspiratory pressure measured at the mouth
PI_{max}	maximal inspiratory pressure measured at the mouth
PR	pulmonary rehabilitation
RV	residual volume
TF-IMT	target-flow inspiratory muscle training
tgF_cDIA	parameter of EMG-fatigability of the diaphragm
tgF_cIC	parameter of EMG-fatigability of the intercostal muscles
TTiDIA	tension-time index of the diaphragm
TLC	total lung capacity
$\dot{V}CO_2$	carbon dioxide output
VD/VT	dead space/tidal volume ratio
$\dot{V}E$	expired minute ventilation
$\dot{V}E_{max}$	maximal minute ventilation
$\dot{V}E/\dot{V}O_2$	ventilatory equivalent for oxygen
$\dot{V}O_2$	oxygen uptake
$\dot{V}O_{2,max}$	maximal oxygen uptake

CHAPTER 2

CHRONIC OBSTRUCTIVE PULMONARY DISEASE: FUNCTIONAL CAPACITY WITH THE EMPHASIS ON THE INSPIRATORY MUSCLES

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2-1. DEFINITIONS AND ASSESSMENT IN COPD

Chronic obstructive pulmonary disease (COPD) is a disorder characterized by a chronic partially irreversible expiratory airflow limitation (1). COPD consists of three disorders: emphysema, peripheral airways disease, and chronic bronchitis. One or more of these conditions may be present in one patient.
Emphysema is characterized by abnormal, permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls, and without obvious fibrosis (2).
Peripheral airways disease in COPD patients consists of inflammation of the terminal and respiratory bronchioles, fibrosis of airway walls with narrowing, and goblet cell metaplasia of the bronchiolar epithelium (3). These lesions contribute to the airflow limitation in severe COPD, but their importance is secondary to that of emphysema.
Chronic bronchitis is defined as chronic or recurrent excess of mucus secretion into the bronchial tree, occurring on most days for at least three months of the year during at least two successive years (1). In these patients there is hyperplasia of the mucus glands of the trachea and large bronchi, and excess of sputum production.

COPD is primarily diagnosed by clinical assessment. The most important complaint is dyspnea on exertion, but in later stages also at rest. Dyspnea is frequently accompanied by wheezing, cough, sputum production, and recurrent infections. Physical examination may reveal signs of lung hyperinflation, increased respiratory muscle effort, and, on auscultation, wheezes and diminished breath sounds. Roentgenographic examination frequently shows hyperinflation, vascular attenuation and bullous lesions.

2-2. PULMONARY FUNCTION

Pulmonary function testing confirms the diagnosis of COPD. The spirometric abnormalities associated with COPD are a reduction in the forced expiratory volume in one second (FEV_1) and in the ratio of the FEV_1 to the inspiratory vital capacity (IVC). The reversibility to bronchodilators is usually low. Frequently there is an increase in the total lung capacity (TLC), residual volume (RV) and functional residual volume (FRC). COPD is also associated with abnormalities in the lung mechanics. The lung compliance may be increased, indicating the presence of emphysema.

A reduction in the diffusion capacity of carbon monoxide (K_{CO}) is an indication of alveolar destruction, which is present in emphysema. There is a ventilation-perfusion mismatch, resulting in shuntlike phenomena at rest, mostly decreasing during exercise. Dead space/tidal volume ratio (VD/VT) is increased, which diminishes the alveolar ventilation. Arterial blood gas analysis gives an insight in a possible impairment in the efficiency of oxygen uptake and/or carbon dioxide elimination.

2-3. EXERCISE CAPACITY

2-3.1. General aspects

The pulmonary function disturbances in COPD lead to dyspnea at exercise and in advanced stages of the disease also at rest. Dyspnea limits patients in their activities, which may lead to a vicious circle of increasing inactivity, resulting in a further decrease of the physical condition. Complications such as exacerbations of the bronchitis, hypoxemia, polycythemia, cor pulmonale and congestive heart failure also induce a state of hypoactivity.

It is important to make an accurate assessment of the patient's exercise capacity and to determine which pathophysiological mechanisms contribute to the decreased exercise capacity. Both questions can be answered by means of a maximal exercise test. In this way a realistic goal can be set before starting a pulmonary rehabilitation program, and it will be clear if specific forms of rehabilitation (e.g. inspiratory muscle training, exercise training with supplemental oxygen) should be considered.

2-3.2. Limiting factors in the exercise capacity

There are several mechanisms by which COPD patients are limited in their exercise capacity (Table 2-1). These are:

- <u>A diminished physical fitness</u>

COPD patients may have a diminished physical fitness, without disturbances or limitations in the pulmonary gas exchange during exercise, just like normal subjects. These patients are limited by the cardiocirculatory capacity of oxygen transport to the tissues, mostly in combination with metabolic limitations at the level of muscle tissue itself. During exercise no disturbances or limitations in the pulmonary gas exchange are present. The heart rate at maximal exercise will be the same as, or exceed the predicted maximal heart rate (220 minus age). Blood lactate will increase (and base excess will decrease) with 10 mmol/l or more. At maximal exercise healthy persons and patients with mild COPD have a reserve in their ventilatory capacity. The expiratory minute ventilation ($\dot{V}E$) at maximal exercise ($\dot{V}E_{max}$) remains lower than the predicted maximal ventilation (MVV predicted, 37.5 x FEV_1) (4). Therefore, the breathing-reserve, defined as the predicted MVV minus $\dot{V}E_{max}$, remains positive. In general, these COPD patients will have minor airflow obstruction.

- <u>A ventilatory limitation</u>

These patients are not able to maintain an adequate alveolar ventilation during incremental exercise. This will result in an increase in the arterial PCO_2 ($PaCO_2$) and a decrease in the arterial PO_2 (PaO_2). The alveolar-arterial PO_2 difference ($D(A\text{-}a)O_2$) does not increase by more than 2 kPa above the value at rest (5). The predicted maximal heart rate will generally not be attained. The breathing reserve will be decreased or even negative at the maximal work load. These patients mostly have moderate to severe airflow obstruction (FEV_1 usually around 50 per cent of predicted). The mechanisms of a ventilatory limitation during exercise will be discussed in detail in section 2-5.

	PaO_2	$PaCO_2$	$D(A-a)O_2$	HR	$\dot{V}E_{max}$	$PI_{pl}max$ $PE_{pl}max$
CARDIOCIRC. LIMITATION	=	↓	↑ <2kPa	$\geq HR_{max}$	<MVV	not reached
V/P MISMATCH	↑/=	=	↓/=	$\leq HR_{max}$	<MVV	not reached
VENTILATORY LIMITATION	↓/=	↑	↑ <2kPa	$<HR_{max}$	<or>MVV	may be reached
DIFFUSION LIMITATION	↓	=	↑ >2kPa	$<HR_{max}$	<MVV	may be reached
MECHANICAL LIMITATION	=	=	↑ <2kPa	$<HR_{max}$	<MVV	reached

Table 2-1. Changes in parameters during a maximal incremental exercise test in COPD patients in relation to values at rest. $D(A-a)O_2$: alveolar-arterial O_2 difference; HR: heart rate; HR_{max}: 220-age (years); $\dot{V}E_{max}$: maximal minute ventilation; $PI_{pl}max$: maximal inspiratory pleural pressure; $PE_{pl}max$: maximal expiratory pleural pressure. MVV: maximal voluntary ventilation, 37.5 x FEV_1; V/P: ventilation-perfusion ratio. Compared to values at rest: = no change; ↑ increased; ↓ decreased.

- <u>A diffusion disorder</u>

This is caused by a reduction of gas exchanging surface area of the lung parenchyma. Since oxygen transport is diffusion-limited in these patients, the arterial PO_2 decreases during the increased oxygen consumption at exercise. The $D(A-a)O_2$ increases more than 2 kPa above the value at rest (5). $PaCO_2$ decreases or remains unchanged. The predicted maximal heart rate is not reached. These patients mostly have emphysema with severe airflow obstruction.

- Impaired respiratory mechanics

The bronchial obstruction and the dynamic airway compression in emphysema require an increased effort of the respiratory muscles during the high ventilatory levels of exercise. The maximal forces generated by these muscles, can be measured from the maximal inspiratory and expiratory pleural pressures. When these maximal pressures are reached during exercise, this can be interpreted as a sign of impending mechanical failure of these muscles. The increased work of breathing causes an intense sensation of dyspnea and will also limit the exercise capacity. Frequently impaired respiratory mechanics are accompanied by a ventilatory limitation or a diffusion disturbance.

- Miscellaneous factors

The exercise capacity in COPD patients may be reduced not primarily due to pulmonary factors, but to e.g. cardiovascular disturbances (myocardial ischemia, disturbances in the cardiac rhythm) and orthopedic or neurological problems.

In COPD patients there is frequently a ventilation/perfusion mismatch, resulting in a lowered PaO_2 at rest. During exercise the mutual relation between ventilation and perfusion improves, resulting in an increase in the PaO_2.
One of the tools of a pulmonary rehabilitation program is, therefore, to make an assessment of the limiting factors in the individual patient in order to realize an adequate training program.

2-4. PSYCHOLOGICAL FACTORS

Psychological factors may influence the individual experience both of symptoms as dyspnea and of diminished validity. It is not clear whether COPD patients differ in psychological characteristics from other chronically sick patients (e.g. patients with rheumatoid arthritis). This is because the various

patient populations that are described in the literature were not always well matched as for age, degree of disability and economic and social status (6). The severity of the illness and not the type of illness, seems to correlate best with the degree of psychological distress (7).
What troubles COPD patients most of all, are anxiety and depression. Dyspnea causes fear, and fear itself generates hyperpnea and dyspnea. The patient may react with an active orientation (anger, anxiety), or with a non-active orientation (depression, apathy, fatigue) (6).
The social status of the patient will be affected when the disease is severe enough to limit physical activities and when psychological factors like anxiety and depression are pronounced. There will be loss of personal relationships. Self-image and self-esteem (social, vocational, sexual, cognitive and physical) will be negatively influenced.

Physical disability and psychosocial factors influence each other. A reduced physical ability leads to inactivity. The physical fitness will further decrease. A new attempt to physical activity will sooner lead to dyspnea. In this way there is a downward spiral, leading to a point of total disability and inactivity. There is no clear relationship between the severity of anxiety and depression on one hand and the functional capacity as measured by means of a twelve-minute walking test on the other (8). However, these psychological factors are significantly related with scores on daily activities (9).
Individual characteristics and social support will determine to what extent the patient may cope with the physical and psycho-social losses. The better the patient can cope with these losses, the better the interindividual behaviour and the response to therapy will be (10).
The major targets in a pulmonary rehabilitation program are, therefore, to increase the physical abilities, to decrease symptoms and to improve the psychosocial well-being.

2-5. VENTILATORY LIMITATION: THE ROLE OF THE RESPIRATORY MUSCLES

2-5.1. Introduction

Respiratory failure is defined as the condition in which the gas exchange in the lungs is insufficient for the metabolic demands of the organism. The results of respiratory failure are expressed in the arterial blood gas analysis: PaO_2 is less than 8 kPa and/or $PaCO_2$ is more than 6 kPa.

A raised $PaCO_2$ indicates a failure of the respiratory pump to maintain a normal alveolar ventilation. Major causes of ventilatory pump failure are:

-a- an inadequate output of the respiratory centres;

-b- lesions of the upper motoneurons, the anterior horn cell, lower motoneurons, or lesions at the neuromuscular junction;

-c- weakness and fatigue of the respiratory muscles, i.e. they are no longer capable of continuously generating adequate negative pleural pressure changes during respiration, despite an appropriate central respiratory drive and an unimpaired chest wall;

-d- loss of elasticity of the lungs or the chest wall or loss of the structural integrity of the chest wall;

-e- an increased airway resistance.

In COPD patients, the major causes of ventilatory failure are the increased airway resistance (which reduces the ventilatory capacity), and weakness and fatigability of the inspiratory muscles.

Most of the work of breathing is performed by the inspiratory muscles. These muscles have the constant task of maintaining a high FRC, both during inspiration and expiration (11). Superimposed are the efforts for every inspiration. The work capacity of the inspiratory muscles is decreased due to weakness of these muscles and to the shift at the length-tension curve, which is caused by the high FRC. The expiration is obstructed by the intrinsic properties of the airways and the lung parenchyma.

The expiratory muscles are not the primary limiting factor during exercise in COPD patients (12).

2-5.2 Function of the respiratory muscles

2-5.2.1. The diaphragm

The diaphragm consists of two parts. The costal part has an axially orientated cylindrical margin, composed of muscle fibres inserted caudally in the inner aspect of the lower rib cage, and constitutes the "area of apposition" (13). The crural part consists of the arcuate ligaments and the muscle fibres inserted in the three upper lumbar vertebral bodies. These two parts converge on the central, non-contractile tendon. There are only few muscle spindles in the diaphragm. Therefore, the diaphragm hardly has a load-compensating reflex when there is an increased work load, in contrast to the intercostal muscles (15).
When the costal part of the diaphragm contracts, the central tendinous part will be displaced caudally for about 2 cm. When the abdominal pressure is sufficiently increased, the lower ribs will be displaced outward and upward (the insertional force) (15). The lower ribs will also be displaced outwards via the area of apposition (appositional force) (Figure 2-1) (13,15). The crural part of the diaphragm also moves the central tendinous part downwards.

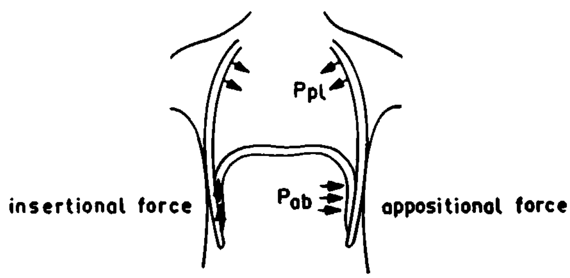

Figure 2-1. Frontal section of the respiratory system at FRC. The appositional and the insertional force displace the lower ribs outwards and upwards. P_{pl}: pleural pressure; P_{ab}: abdominal pressure.

At FRC level, the costal and crural parts are coupled parallelly, i.e. the total pressure generated by the diaphragm is the sum of the pressures generated by the two parts separately. During inspiration, the two parts will be coupled in series. Consequently, the total generated pressure then is the pressure of one of the two parts (16).

2-5.2.2. The intercostal muscles

The external intercostal muscles run from lateral-proximal to medial-distal between the ribs. The internal intercostal muscles have an opposite direction. The parasternal intercostal muscles are a fusion of the external and internal intercostal muscles. The first four parasternal intercostal muscles are active during inspiration (17). Isolated contraction of these muscles causes a lateral movement of the ribs and a downward movement of the sternum. The interossal intercostal muscles have a postural function (18). In contrast to the diaphragm, the intercostal muscles contain a substantial amount of muscle spindles. These spindles make monosynaptic spinal load compensating reflexes possible (14).

2-5.2.3. The scalene muscles

The anterior, medial, and posterior scalene muscles run from the processi transversi of the cervical vertebrae C1-7 to the first and second rib. The scaleni are active during breathing at rest in normal subjects. Contraction of the scaleni results in anteroposterior and lateral movement of the thorax via cranial movement of the sternum and the ribs.

2-5.2.4. Length-tension relationship

An important property of skeletal muscles is their length-tension relationship (Figure 2-2). At a given neural stimulus a muscle generates its maximal tension at approximately its resting length. When the lung volume is increased, the diaphragm contracts from a shorter end-expiratory length and will generate less pressure. The parasternal intercostal muscles, however, will shift towards their optimal resting length in hyperinflation. Therefore, especially the function of the diaphragm will be negatively influenced in hyperinflation.

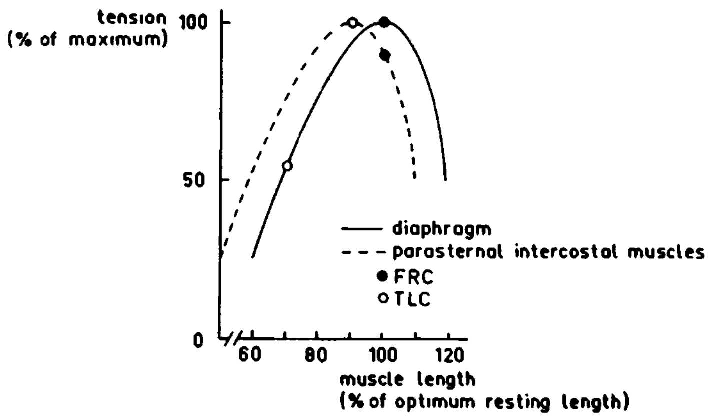

Figure 2-2. Length-tension relationship of the diaphragm and the parasternal intercostal muscles.

2-5.2.5. Effects of the abdominal muscles during breathing

Contraction of the abdominal muscles will displace the ribs downwards; this is an expiratory function. The transversus abdominis is most important in this action (19).

The abdominal muscles also have an indirect inspiratory function. During contraction of the abdominal muscles, the abdominal pressure will increase and the lower ribs will be displaced outwards via the area of apposition. When the intensity of breathing increases, there is an increase of the activity of the transversus abdominis and the rectus abdominis during expiration. This will increase the expiratory flow and optimize the diaphragmatic function by placing the diaphragm at the optimal part of its length-tension curve.

2-5.3. The respiratory muscles in COPD

In patients with COPD the length of the diaphragm at RV and at FRC is shortened compared to normal subjects (20). Therefore, less tension can be generated at a given length. Compensatory resorption of sarcomeres may result in a shift of the length-tension curve towards a smaller optimal resting length. This phenomenon has been demonstrated in elastase-induced emphysema in hamsters (21), but not in humans (22).

This shortening of the diaphragm will render it less efficient as a pressure generator. Moreover, at higher lung volumes the costal and crural part of the diaphragm will be coupled in series, which also negatively affects the pressure-generating ability of the diaphragm. The diaphragm may then only act as a fixator by isometric contraction. In the case of even more hyperinflation, contraction of the diaphragm may lead to an inward movement of the lower ribs during inspiration (Hoover's sign).

The parasternal intercostal muscles will shift towards an optimal resting length in hyperinflation. The resting length of the mm. scaleni and mm. sternocleidomastoidei is hardly affected by hyperinflation.

Besides the mechanical disadvantage consequent to the increased lung volume, in some COPD patients the respiratory muscles are weak (20). This will contribute to the decreased work capacity of the inspiratory muscles.

The (hypothetic) balance between the capacity of the inspiratory muscles and the work load of breathing is shown in Figure 2-3.

The result of these changes is a more pronounced thoracic breathing pattern. This is confirmed by the findings of Sanchez et al (23): in biopsies of the intercostal muscles of patients with COPD they found more oxidative and glycolytic enzyme activity than in normal subjects.

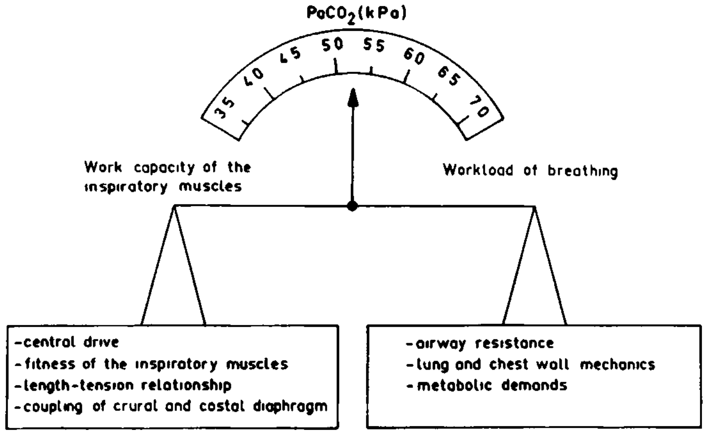

Figure 2-3. Factors that influence the balance between the work capacity and the work load of the inspiratory muscles.

2-5.4. Fatigue and failure of the inspiratory muscles

Skeletal muscle fatigue is defined as a functional state of the muscle in which there is a reduction in the capacity to generate maximal force, recoverable by rest. Fatigue may be the result of failure at any site on the motor path: the central nervous system (central fatigue), failure of the electrical or chemical neuromuscular transmission (neuromuscular junction failure), and failure of the muscle itself (peripheral fatigue).
Mechanical changes in a fatiguing muscle are:

1- a decline of maximal force during a constant isometric contraction after a certain time;
2- a decline of the relaxation rate in the course of time of contraction (24);
3- a shift of the force-frequency curve of the fatigued muscle to the right, so that less force is produced at a given frequency of <u>external</u> stimulation; the recovery of force generation is faster after high-frequency stimulation than after low-frequency stimulation.

The electromyogram (EMG) changes during a fatiguing contraction. The total integrated EMG power for a given muscle force increases. There is a shift in the power spectrum from higher to lower intrinsic frequencies during the course of a fatiguing contraction. This can be measured by a shift in the high-to-low ratio and in the median (centroid) frequency (F_c) of the power spectrum (25). There is a linear relationship between the EMG changes and the duration of the fatiguing contraction, starting directly from the beginning of this contraction (26). They precede the mechanical signs of fatigue. The EMG changes are reversible when the muscle rests.

Skeletal muscles sustaining a continuous contraction will fatigue when the generated force is above fifteen per cent of its maximal force. During intermittent contraction the critical force above which fatigue will develop, varies as a function of the ratio of the duration of contraction and the total duration of the cycle of contraction and relaxation. For the respiratory muscles this ratio is called the duty cycle.

The transdiaphragmatic pressure (Pdi) can be expressed as a fraction of the maximal Pdi (Pdi_{max}). The Pdi that can be sustained indefinitely, was found to be inversely related to the duty cycle. The product of these two variables (Pdi/Pdi_{max} and the duty cycle) is the tension-time index of the diaphragm (TTiDIA) (Figure 2-4) (26). Bellamare (26,27) showed that the diaphragm will fatigue when TTiDIA is more than 0.15. Below 0.15 fatigue did not develop (26,27).

Patients with COPD run a higher risk of developing inspiratory muscle fatigue than normal subjects. In terms of Pdi/Pdi_{max} and the duty cycle, there are clear differences between COPD patients and normal subjects. Normal subjects breathe with a tension-time index of about 0.02 at rest and thus have a large (sevenfold) reserve before reaching the fatigue treshold.

COPD patients have a decreased Pdi_{max} and an increased tidal Pdi, thus Pdi/Pdi_{max} is increased. Their duty cycle tends to be smaller than normal. Bellamare and Grassino (28) studied the tension-time index in 20 COPD patients at rest. The tension-time index varied from 0.02 to 0.12 (average 0.055). So the (threefold) functional reserve of the diaphragm is lower than in normals. When the airflow resistance increases, tidal Pdi will increase and fatigue will ensue more easily (28).

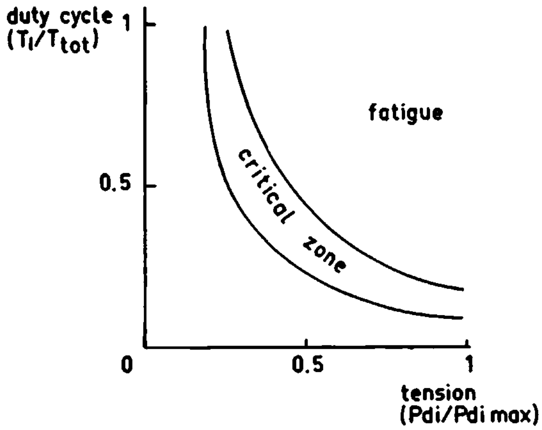

Figure 2-4. The relationship between the tension (Pdi/Pdi_{max}) and the duration of the inspiration as a fraction of the duration of the total respiration (duty cycle, T_i/T_{tot}) of the diaphragm.

Other factors than Pdi/Pdi_{max} and the duty cycle, however, also influence the performance of the diaphragm. The resting length of the diaphragm, the velocity of shortening during contraction and the energy supply are important determinants of the work load of the diaphragm and may contribute to the development of fatigue. Therefore, an exact margin above which fatigue will develop, is difficult to determine.

These factors result in an increased fatigability of the inspiratory muscles and can lead to failure to maintain an adequate alveolar ventilation. This occurs especially in conditions in which the work load of the inspiratory muscles is increased, such as in exacerbations or during exercise.

2-6. PULMONARY REHABILITATION

2-6.1. Introduction

Pulmonary rehabilitation (PR) is defined as an art of medical practice in which an individually tailored, multidisciplinary program is formulated. It is indicated for patients suffering from complex problems in relation to their pulmonary disease. The aims of PR are to reverse symptoms, functional limitations and psychological and social consequences of the pulmonary disease and to return the patient to the highest possible functional capacity allowed by his pulmonary disturbance and overall situation (1).

A PR program contains accurate diagnosis, optimalization of medical treatment, physical exercises, breathing retraining and education. Moreover psychological and social support may be necessary.

Physical exercises are aimed at an improvement of the cardio-circulatory performance, an increase in the suppleness and coordination, an improvement of the metabolism of the muscles and an increase in the strength and endurance of the skeletal muscles like the major muscle groups and the inspiratory muscles.

2-6.2.1. General exercises

The intensity of physical exercises that causes a training effect in subjects with a cardiocirculatory limitation of their exercise capacity depends on the initial physical fitness of the subject. A training intensity above 50 per cent of the subject's maximal aerobic power will be sufficient to produce a significant training effect and should gradually be increased to 70-80 per cent of the individal maximal work power (30).

Training in normal subjects results in a reduced heart rate at comparable submaximal levels of exercise (31). An improved technique or efficiency will result in a lowered $\dot{V}O_2$ at that level of exercise. $\dot{V}O_{2,max}$ will increase with ± 5-20 per cent, depending on the intensity of the training and the initial state of fitness of the subject (30). The transport of O_2 from the muscle capillary to the mitochondrial enzymes is facilitated after training. This is caused by an increase in capillary density, myoglobin content and mitochondrial size and number in the trained muscles.

2-6.2.2. General exercises in COPD

There are several mechanisms by which physical training may improve the exercise capacity in COPD patients, depending on the type of limitation in the individual patient:

1- In patients with a cardiocirculatory limitation, general exercise training may improve the aerobic capacity, as measured by an increased $\dot{V}O_{2,max}$. However, most COPD patients are not able to perform such an exercise that an increase in $\dot{V}O_{2,max}$ will occur. Moreover, while performing an incremental exercise test, the COPD patient will often stop because of the subjective feeling of dyspnea. So, if training could result in an increased tolerance of dyspnea, the patient will be less disabled and can perform higher work intensities, expressed by a higher $\dot{V}O_{2,max}$. This does not necessarily reflect an increased aerobic capacity.

2- Increased motivation or self-confidence will lead to a reduction in the impairment and thus to improvement of the exercise capacity. This can be measured from a higher $\dot{V}O_{2,max}$, $\dot{V}E_{max}$ or maximal heart rate.

3- Decrease of the dyspnea sensation may also contribute to an increased exercise performance.

4- An improved mechanical skill will decrease the oxygen cost of work and the ventilatory requirement, although the work load is unchanged. This implies an increased efficiency in performing a certain work load.

5- The performance of the inspiratory muscles may improve. In patients with a ventilatory limitation during exercise, in which fatigue and failure of the inspiratory muscles contribute to the reduction of the exercise capacity, strength and endurance of these muscles can be increased by general exercises or specific inspiratory muscle training.

Exercise training in COPD patients results in an increased work capacity. The twelve-minute walking distance increases after a training program, varying from ± 6 to 25 per cent in the various studies (32,34,35). The work load during an incremental exercise test increases by ± 8-25 per cent (32,34,35), although it is not clear to what extent the exercise tests were really maximally performed. Routine activities in every day life are performed more easily (36). Respiratory symptoms decrease (37,38) and there is reduction in hospitalization (39).

2-6.3. Inspiratory muscle training

The inspiratory muscles can be trained like other striated muscles, in order to increase their strength and/or endurance. This has been shown in healthy subjects (40,41), in patients with cystic fibrosis (41,42), in quadriphlegics (43) and in patients with COPD (44-55). Three methods of inspiratory muscle training (IMT) have been described:

1- Normocapnic hyperpnea: sustained voluntary ventilation may be applied to patients with COPD (49). Because of the elaborate experimental set-up, this kind of training can only be performed in the laboratory.

2- Resistive breathing: in this type of training the patient breathes through an external inspiratory resistance; the expiration is unloaded. Several devices are commercially available.

3- Threshold-loaded breathing: this is a modification of resistive breathing, in order to ensure a sufficient inspiratory pressure to be generated before air starts to flow (50,56,57).

In resistive breathing it is important to determine the generated inspiratory pressure and/or the inspiratory flow, as well as the duration of the inspiration and expiration, in order to provide an adequate training stimulus to the inspiratory muscles. If these parameters are not controlled, the subjects will develop a breathing pattern with a low inspiratory flow in order to evade the (flow-dependent) inspiratory resistance (i.e. adopt a breathing pattern with a low tension-time index).

In several studies on IMT the maximal inspiratory mouth pressure (PI_{max}) increased significantly (47,51,52,58). In another study no improvement of PI_{max} was observed (45). Probably, this reflects the intensity of the training stimulus. Inspiratory muscle endurance increased, as measured by the inspiratory resistance that could be tolerated after the training period (45,51,53).

The effects of IMT on the general exercise capacity in COPD patients are controversial. An improvement was detected in several studies (49,44,52, 54,58). In other reports, however, no effects on the physical condition were measured (48,52,53).

In one study (47) the effects of IMT during a PR program were studied. Thirteen COPD patients participated in a physical training program (cycling for twenty minutes, three times a week). Additional IMT in seven of these patients resulted in an increase in endurance and strength of the inspiratory muscles, whereas the general exercise capacity did not increase compared to physical training alone.

The following remarks may be made about the studies on IMT:

1- There was <u>no selection criterion</u> by which COPD patients should train their inspiratory muscles or not. Only Noseda et al (56) selected COPD patients on the basis of a ventilation at maximal exercise that exceeded the maximal voluntary ventilation.

   It is our hypothesis that IMT should be applied to those COPD patients who are limited in their exercise capacity because of fatigue and failure of their inspiratory muscles when the metabolic demands increase. Consequently, the final criterion is an increase in $PaCO_2$ during a maximal exercise test. Only in one study (45), a (retrospective) distinction was made between COPD patients with and without signs of fatigue and failure of their inspiratory muscles. It appeared from this study that especially those patients who showed (EMG-) signs of fatigue of their inspiratory muscles, benefited most from IMT, demonstrated by an increase in endurance of these muscles and submaximal exercise levels.

2- The method of training, especially resistive breathing, is not standardized. In most studies the generated inspiratory mouth pressure, inspiratory flow and the duration of inspiration and expiration were not determined. Subjects may thus adopt a non-fatiguing breathing pattern with a low inspiratory flow and pressure. Therefore, it is not certain to what extent a sufficient training stimulus was given to the inspiratory muscles.

3- In most studies it is not clear if IMT was regularly supervised. In that situation it cannot be established if the subjects really trained their inspiratory muscles.

4- The number of patients in the different studies was small, varying from 4 (57) to 32 (48).

5- The duration of the training program was rather short, varying from 6 weeks (49,54,55) to 3 months (46).

6- To our knowledge, there are no studies about a follow-up period after the training period.

2-7. CONCLUSIONS

The inspiratory muscles in patients with COPD may become fatigued due to the increased work load (airflow obstruction), and their mechanical disadvantages in performing this work (hyperinflation), sometimes combined with weakness. This may limit these patients in their exercise capacity. During exercise tests a ventilatory limitation will be found in these patients, i.e. a normal resting $PaCO_2$ that rises during incremental exercise.

Pulmonary rehabilitation may result in an increased work capacity, which can be caused by increased skills, a better performance of the inspiratory muscles and sometimes by an increase of the aerobic power.
The effects of specific inspiratory muscle training are controversial. It seems that inspiratory muscle strength and endurance can be increased. The effects on the general exercise capacity are not clear. Factors that may contribute to these controversies are a non-specified patient selection in most studies, and a poorly defined training method which may not always result in an adequate training stimulus.

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CHAPTER 3

TARGET-FLOW INSPIRATORY MUSCLE TRAINING: BREATHING PATTERN AND METABOLIC COSTS

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3-1. INTRODUCTION

The inspiratory muscles (IM) may become fatigued when they are exposed to an increased work load and when their ability to perform this work is reduced. Fatigue of the IM may occur in normal subjects while breathing through a high resistance (1,2), and during exercise in patients with chronic obstructive pulmonary disease (COPD) (3).

Inspiratory muscle training (IMT), by breathing through an inspiratory resistance, has been used to increase strength and endurance of the IM (4-9). In currently applied IMT the inspiratory effort is not controlled and the subjects may develop tactics to breathe through the resistance with a minimal effort by breathing with a low respiratory frequency or with a low inspiratory flow rate (10). Consequently, an adequate training stimulus to the IM is absent and a training effect will not be achieved.

In order to standardize the applied training stimulus, a training method is described in which the generated inspiratory mouth pressure (PI) and the duration of inspiration and expiration are controlled.

One of the effects of IMT might be a more efficient breathing pattern during and after IMT, e.g. a decrease in the ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) or in dead space/tidal volume ratio (VD/VT).

Some studies indicate that the metabolic costs during IMT were increased significantly in normal subjects (11,12). However, it is not certain to what extent COPD-patients differ from normal people in their metabolic demands during IMT or whether IMT leads to a respiratory insufficiency with increased PCO_2 levels.

The aims of this study were to investigate whether the breathing pattern changed during and after standardized target-flow inspiratory muscle training (TF-IMT) and whether blood lactate or the PCO_2 changed during TF-IMT, both in normal subjects and in patients with COPD. Furthermore, the effect of this training method on inspiratory muscle strength was measured from the maximal inspiratory mouth pressure (PI_{max}) after a ten-week training period of TF-IMT in a group of COPD patients with a ventilatory limitation of their exercise capacity.

3-2. METHODS

3-2.1. Selection of subjects

a) Control group: fifteen non-smoking volunteers (eight men, seven women, mean age 30) were selected. None of them had pulmonary complaints or abnormal lung function tests.

b) COPD group: twelve COPD-patients (eight men, four women, mean age 58) were selected. All patients had a ventilatory limitation of their exercise capacity, i.e. their resting arterial PCO_2 was normal and increased during a maximal bicycle ergometer test. This may indicate an insufficiency of the inspiratory muscles to maintain an adequate alveolar ventilation during the higher metabolic rate of exercise. None of them had a diffusion disorder, i.e. there was no significant lowering of the arterial PO_2 during incremental exercise. There were no other limitations of the exercise capacity, like cardiac or neuromuscular diseases. They had been clinically stable during the last three months before the experiment.
Informed consent was obtained from all subjects.

3-2.2. Lung function

Spirometry was performed with a wet spirometer (Pulmonet III, Gould-Godart). Total lung capacity (TLC) was measured by the closed circuit helium-dilution method (Pulmonet III). The diffusion capacity for carbon monoxide (K_{CO}) was measured by the single breath-holding carbon monoxide method (Morgan).
PI_{max} from residual volume was measured with a pressure transducer (Validyne). Four to seven measurements were performed and the highest value was taken for the PI_{max}.

3-2.3. Experimental design and measurements

The experimental set-up is shown in Figure 3-1. During the experiment the subject was seated in upright position. TF-IMT was performed by means of a simple disposable incentive flowmeter (Inspirx, Intertech Resources Inc.), modified by adding a resistance with an orifice of an internal diameter of 2 mm. into the mouthpiece.

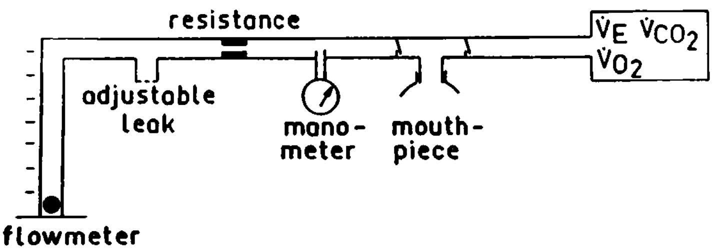

Figure 3-1. Experimental set-up. The subject was instructed to inspire with such an effort that the ball in the flowmeter reached the top, corresponding with an inspiratory pressure of 70 per cent of PI_{max}. $\dot{V}E$: minute ventilation; $\dot{V}O_2$: oxygen consumption; $\dot{V}CO_2$: carbon dioxide output.

The experimental protocol was as follows: after unloaded breathing (baseline) during five minutes (T=0-5), the subjects inspired through the resistance during fifteen minutes (T=6-20). After this period, there was a recovery phase of five minutes (T=21-25).

The subjects were instructed to create an inspiratory flow rate at which the ball in the flowmeter reached the top of the device (the target-flow). The adjustable leak in the flowmeter was set by the experimenter, so that the subjects had to generate 70 per cent of their PI_{max} in order to keep the ball at the top of the flowmeter. The subjects could adjust their inspiratory effort themselves by reading the flowmeter. The duration of the inspiration (T_i) was set at three seconds by means of a metronome, the (unloaded) expiration (T_e) at four seconds. The

respiratory frequency therefore was eight to nine breaths per minute. The duration of the TF-IMT experiment was fifteen minutes.
During the experiment, the generated mouth pressure was continuously measured and recorded by means of a pressure transducer. The modified incentive flowmeter with the individually adjusted leak was attached to the inspiratory side of a Hans-Rudolph valve. The expiratory side of this valve was connected to an analyser of minute ventilation ($\dot{V}E$), oxygen uptake ($\dot{V}O_2$), and carbon dioxide output ($\dot{V}CO_2$) (Oxycon IV, Mijnhardt). During the experiment every 30 seconds an output was produced of $\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$ and ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$).
At T=4, T=19, and T=24, an arterialised capillary blood sample was obtained for blood gas analysis (Ciba Corning 178 DMS) and for measurement of lactate (Enzymatic UV-test, Boehringer Mannheim).
Heart rate and peripheral oxygen saturation were monitored with a pulse oxymeter (Oxyshuttle; SensorMedics).
The physiological dead space was calculated by the Bohr equation and expressed as a fraction of the tidal volume (VD/VT).
After completing these measurements, the COPD patients participated in an inspiratory muscle training program, which consisted of standardized TF-IMT during fifteen minutes twice a day for a period of ten weeks. PI_{max} from residual volume was measured weekly during the training period.

3-2.4. Data analysis

A Wilcoxon test was used to compare the data within the two groups at rest, during TF-IMT and in the recovery period per group. The results of the two groups were compared by means of the U-test of Mann and Whitney. P-values of less than 0.05 were considered to be significant.

3-3. RESULTS

The characteristics of the patients are presented in Table 3-1. All patients had moderate to severe airflow obstruction.

age, yrs	58.2	(8.5)
TLC, %pred	106.2	(12.4)
FEV_1, L	1.17	(0.42)
FEV_1, %pred	46.2	(13.4)
FEV_1/IVC, %	35	(7)
K_{CO}, %pred	72	(24)

Table 3-1. Patient characteristics (means (SD); n=12). K_{CO}: diffusion capacity for carbon monoxide.

Ventilatory parameters

The changes in ventilatory and metabolic parameters are shown in Table 3-2. $\dot{V}E$ at rest, during TF-IMT and during recovery was significantly higher in the COPD group than in the control group. In the COPD group, $\dot{V}E$ decreased significantly during TF-IMT. During TF-IMT $\dot{V}O_2$ increased significantly only in the control group. The $\dot{V}CO_2$ did not change during the experiment in either of the groups.

$\dot{V}E/\dot{V}O_2$ at rest was higher in the COPD group than in the control group ($p<0.01$) (Figure 3-2). In both groups there was a significant decrease in $\dot{V}E/\dot{V}O_2$ during TF-IMT, in the recovery period returning to the baseline value in the control group, but not in the COPD group. The same tendency was seen in the course of VD/VT (Figure 3-3). At rest VD/VT was higher in the patients than in the controls ($p<0.01$). After a decrease during TF-IMT, VD/VT remained below the baseline value in the COPD group during recovery.

	Patients (n=12)			Controls (n=15)		
	1	2	3	1	2	3
$\dot{V}E$, L/min	12.31 O	9.22**O	9.66*O	9.06	8.15	8.33
$\dot{V}O2$, L/min	0.29	0.31	0.26	0.27	0.31*	0.25
$\dot{V}CO2$, L/min	0.25	0.25	0.23	0.24	0.26	0.24
PH, unit	7.42	7.42	7.41	7.42	7.43	7.42
PCO_2, kPa	5.29	5.38	5.30	5.24	5.23	5.24
BE, mmol/L	1.68	1.87	1.80	1.47	1.94*	1.91
lactate, mmol/L	1.57	1.43	1.46	1.63	1.66	1.64

Table 3-2. Ventilatory and metabolic parameters before, during and after target-flow inspiratory muscle training (TF-IMT) in the two groups. Values are means. 1-baseline, 2 TF-IMT, 3 recovery. Data compared to baseline: * $p<0.05$, ** $p<0.01$. Data compared to controls: O $p<0.01$.

Blood gas data and heart rate

There were no significant changes in pH and blood lactate levels in either group during the experiment (Table 3-2). Peripheral oxygen saturation did not change. PCO_2 increased in the patients from 5.29 kPa to 5.38 kPa during TF-IMT, but this was not significant. In both groups the base excess increased, but only significantly in the control group. In this control group the mean heart rate increased during TF-IMT from 69 to 75 ($p<0.05$) and in the patient group from 79 to 81 (NS).

PI_{max}

PI_{max} values ((means)(SD)) before and after the ten-week training period in the COPD patients were 5.7 (2.2) kPa and 8.2 (2.7) kPa ($p<0.05$) (Figure 3-4).

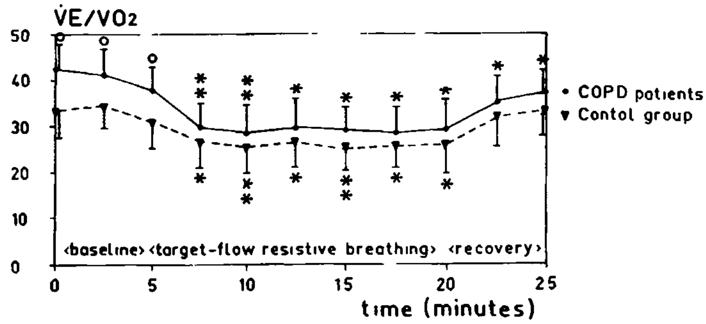

Figure 3-2. Acute changes in ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) during a session of TF-IMT. Data are means + SD. Data compared to baseline: * $p<0.05$, ** $p<0.01$. O compared to controls: $p<0.01$.

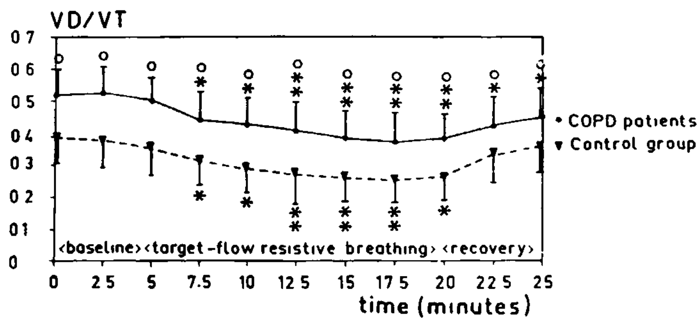

Figure 3-3. Acute changes in dead space/tidal volume ratio (VD/VT) during a session of TF-IMT. Data are means + SD. Data compared to baseline: * $p<0.05$, ** $p<0.01$. O compared to the control group: $p<0.01$.

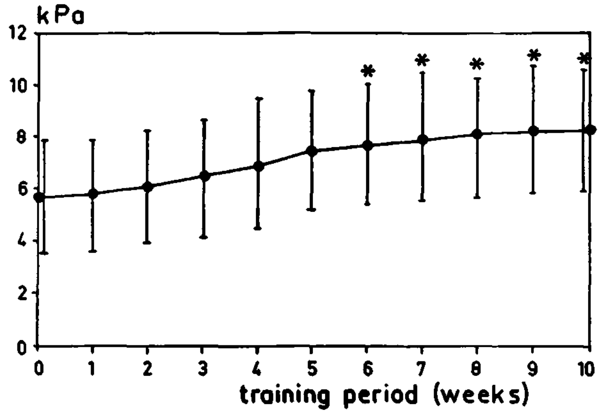

Figure 3-4. Changes in PI_{max} during the ten-week training period of TF-IMT in the COPD group. Data are means ± SD. * $p<0.05$ compared to the start of the training period.

3-4. DISCUSSION

In the COPD patients, $\dot{V}E$, $\dot{V}E/\dot{V}O_2$ and VD/VT decreased during TF-IMT. These effects persisted in the recovery period. In the normal subjects, $\dot{V}E/\dot{V}O_2$ and VD/VT only decreased during the time they used the resistive device, with no significant effect on $\dot{V}E$. PCO_2 and blood lactate did not change significantly in either of the groups.

When training the IM, it has to be assured that a sufficient stimulus is given to improve strength and/or endurance of these muscles. Therefore, the inspiratory pressure or flow and the duration of inspiration and expiration have to be set at a certain level (14). In TF-IMT, the inspiratory pressure-time index at the mouth is 0.3 (PI/PI_{max} = 0.7, T_i/T_i+T_e = 3/7). Roussos (15) has shown that the endurance time was prolonged when the inspiratory pressure-time index during resistive breathing was about 0.3 (PI/PI_{max} = 0.6, T_i/T_i+T_e = ±0.5). All subjects in our study were able to perform this breathing task. A target flow or pressure can be simply imposed by using a simple, inexpensive flowmeter modified with an added resistance and with visual feedback on the PI, as described in our study.

The COPD group had a significantly higher baseline $\dot{V}E$ and $\dot{V}E/\dot{V}O_2$ than the control group, due to a high VD/VT. During TF-IMT, $\dot{V}E$, $\dot{V}E/\dot{V}O_2$ and VD/VT decreased in both groups, without a change in capillary PCO_2. Kelsen et al (10) studied 6 COPD patients who were breathing through a threshold device, so that the generated mouth pressure was between 40 and 60 per cent of PI_{max}. They found similar effects, indicating a decrease in VD/VT. Oliven et al (16) studied a group of twelve COPD patients who were breathing during ten minutes through a flow-resistive load during both inspiration and expiration. PCO_2 increased most in the patients with a very low PI_{max}. Furthermore, this relative hypoventilation might be due to loading the expiration as well as the inspiration.

We did not find a significant change of the capillary blood lactate during TF-IMT. Jardim et al (12) found a small increase of the arterial blood lactate concentration (from 0.8-1.8 mmol/l) in four normal subjects who inspired through a resistance at 80 per cent of PI_{max} till exhaustion. In their study the IM were loaded more heavily than in our experiment. Eldridge (17) showed an increase of blood lactate in normal subjects breathing through an inspiratory resistance with an added dead space, while the inspired oxygen concentration was fifteen per cent. So, it seems that the IM have to be loaded very heavily in order to cause a systemic rise of the blood lactate concentration. This is not surprising, since the IM represent only a small muscle group of about 960 grams (17).

PI_{max} can be considered as an index of the function of the IM as a pressure generator. This parameter increased significantly during the ten-week training period in the COPD patients. This indicates that with TF-IMT the IM were really being trained in these patients in whom it was shown that these muscles fail during exercise. To our knowledge, it is only Pardy et al (6) who

have studied COPD patients selected on the criterion of respiratory muscle fatigue during exercise and who observed more improvement of their exercise capacity than in patients without signs of respiratory muscle fatigue.
It is concluded that the inspiratory muscles in COPD patients with a ventilatory limitation of their exercise capacity can be adequately trained by TF-IMT at 70 per cent of PI_{max} and with a fixed duration of inspiration and expiration. This is expressed in a significant increase in the PI_{max} after a ten-week training period. Moreover, a session of TF-IMT results in a decrease of $\dot{V}E$, $\dot{V}E/\dot{V}O_2$ and VD/VT in the COPD patients, which persists during the recovery period.

3-5. SUMMARY

In target-flow inspiratory muscle training (TF-IMT), the generated inspiratory mouth pressure and the duration of the inspiration and expiration are standardized to give an adequate training stimulus to the inspiratory muscles. The acute effects of TF-IMT on the efficiency of breathing were studied in a group of twelve COPD patients with a ventilatory limitation of their exercise capacity (mean age 58, mean FEV_1 46.2 per cent of predicted) and in fifteen normal subjects (mean age 30). Also, the effect of a ten-week period of TF-IMT on the maximal inspiratory mouth pressure (PI_{max}) in the COPD patients was measured. After an unloaded baseline period, the subjects started to inspire through a target-flow device during fifteen minutes, followed by a recovery phase of five minutes. During TF-IMT minute ventilation ($\dot{V}E$) decreased only in the COPD group. The ventilatory equivalent for O_2 ($\dot{V}E/\dot{V}O_2$) and the dead space to tidal volume ratio (VD/VT) decreased in both groups. During recovery, $\dot{V}E$, $\dot{V}E/\dot{V}O_2$ and VD/VT remained below baseline values in the COPD group, but not in the control group. PCO_2 and lactate concentrations did not change during TF-IMT. After the 10-week training period, PI_{max} ((means)(SD)) increased from 5.7(2.2) to 8.2(2.7) kPa ($p<0.05$).

The results indicate that with standardized TF-IMT, the inspiratory muscles can be trained effectively in COPD patients with a ventilatory limitation. The persistence of the decrease in $\dot{V}E$, $\dot{V}E/\dot{V}O_2$ and VD/VT after a training session may be an additional beneficial effect of TF-IMT.

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CHAPTER 4

TARGET-FLOW INSPIRATORY MUSCLE TRAINING DURING PULMONARY REHABILITATION IN COPD PATIENTS WITH A VENTILATORY LIMITATION DURING EXERCISE

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Submitted for publication

4-1. INTRODUCTION

Inspiratory muscle training (IMT) in patients with COPD can result in an increase of strength and endurance of these muscles (1-7). The effects of IMT on the exercise capacity of patients with COPD are controversial. Some investigators found an increased exercise capacity after IMT (3,5-8), whereas other studies did not reveal such effects (9,10). This bias may be due to an inadequate selection of patients who underwent IMT, or to the method and protocol of IMT. Furthermore, the effects of additional IMT during a pulmonary rehabilitation (PR) program have not been studied yet.

The aim of this study is to investigate whether additional supervised target-flow IMT (TF-IMT) during PR is superior to PR alone in COPD patients with a ventilatory limitation of their exercise capacity, in terms of performance of the inspiratory muscles as well as general exercise capacity.

4-2. METHODS

4-2.1. Design of the study

Forty COPD patients with a ventilatory limitation of their exercise capacity participated in a ten-week PR program. Before entering, they were randomly selected to either receive additional TF-IMT or not. Measurements of inspiratory muscle performance and exercise capacity were made before entering the program, and after four and ten weeks. Informed consent was obtained from all patients.

4-2.2. Patients

Patients with COPD were selected from the outpatient clinic. The characteristics of the patients are shown in Table 4-1. All patients had moderate to severe airflow obstruction without significant changes after inhalation of bronchodilators.

In all of them a ventilatory limitation of their exercise capacity was established by means of a maximal bicycle ergometer test. The ventilatory limitation was defined as a normal resting arterial PCO_2 that rose during progressive exercise. This may indicate an insufficiency of the respiratory muscles to maintain an adequate ventilation during the higher metabolic rate of exercise. Furthermore, their ventilation at maximal exercise ($\dot{V}E_{max}$) was close to their predicted maximal voluntary ventilation (predicted MVV, 37.5 x FEV_1) (11). The alveolar-arterial oxygen difference ($D(A-a)O_2$) did not increase by more than 2 kPa at maximal exercise, so a diffusion disorder was excluded (12). The patients did not have other limitations of their exercise capacity, such as cardiovascular or neuromuscular problems.

4-2.3. Training

- Pulmonary rehabilitation program

For a period of ten weeks the patients participated in the PR program, five days a week, two hours every day. This program consisted of exercise training (cycling, walking, training of back, shoulder and abdominal muscles), callisthenics, conventional physiotherapy (breathing retraining, relaxation exercises) and education about the pulmonary disease and the purpose and use of the medications.

- Target-flow inspiratory muscle training

An incentive flowmeter (Inspirx, Intertech Resources Inc.) with an added resistance was used for TF-IMT. The patients were instructed to generate an inspiratory flow rate at which the ball in the flowmeter reached the top of the device (the target-flow). The adjustable leak in the flowmeter was set by the physiotherapist, so that the patient had to generate 70 per cent of his maximal inspiratory mouth pressure (PI_{max}) in order to keep the ball at the top of the flowmeter. The duration of the inspiration was set at three seconds by means of a metronome, the (unloaded) expiration at four seconds. The respiratory frequency therefore was eight to nine breaths per minute. The patient performed TF-IMT during fifteen minutes twice a day, supervised by the physiotherapist. Twice a week PI_{max} was measured and the target-flow was adjusted to the new PI_{max}.

4-2.4. Measurements

- Lung function

Total lung capacity (TLC) was measured by means of the closed circuit helium-dilution method (Pulmonet III, Gould-Godart). Spirometry was performed with a wet spirometer (Pulmonet III). The diffusion capacity (K_{CO}) was measured by using the single breath-holding carbon monoxide method (Morgan). The semistatic compliance ($compl_{ss}$) was measured by means of a Godart Compliance Test III. Predicted values were derived from Quanjer (13).

- Bicycle ergometer test

A maximal incremental exercise test till exhaustion was performed on an electrically braked bicycle ergometer (Lode). An estimation of the maximal work load (W_{max} pred, watts) was made by the equation: W_{max} pred=1.7 x weight(kg) + 40 x FEV_1(L) -25 (14). Every minute the work load was increased by ten percent of W_{max} pred. Heart rate and peripheral oxygen saturation were monitored with a pulse oxymeter (Oxyshuttle, SensorMedics). An arterial blood sample for blood gas analysis (Ciba Corning 178 DMS) was taken every three minutes and at W_{max}. Every 30 seconds an output was printed of minute ventilation ($\dot{V}E$), O_2-uptake ($\dot{V}O_2$), CO_2-output ($\dot{V}CO_2$) and derived parameters (Oxycon IV, Mijnhardt).
The breathing reserve (BR) was calculated by the predicted maximal voluntary ventilation (MVV, 37.5 x FEV_1) minus ventilation at exercise and was expressed as a percentage of MVV.

- Twelve-minute walking distance

This test was performed in a hospital corridor. The patients were instructed to walk as long a distance as possible during a period of twelve minutes (15). During the test they were continuously encouraged in order to reach a maximal walking distance. Before entering the study, the patients had one training session to become familiar with the test.

- Maximal inspiratory mouth pressure

PI_{max} from residual volume was measured by means of a flanged occluded mouthpiece with a small leak, connected to a manometer (Validyne). The highest value of four to seven maximal inspiratory manoeuvres was taken as PI_{max}. Data were expressed in kPa and as percentage of predicted (16).

- Electromyogram (EMG)

Standard surface electrodes (diameter 5 mm.) with conducting gel were used for the registration of the EMG signals of the diaphragm and the intercostal muscles. For the diaphragm, the electrodes were placed in the 6th and 7th intercostal spaces on the right anterior axillary line (17). The intercostal electrodes were placed in the 2nd and 3rd left intercostal spaces, 2 cm from the edge of the sternum. In order to minimize disturbances of non-respiratory muscles, the patients were lying on a bed with appropriate support for their arms.
The EMG signals were amplified 3,000 to 10,000 times (Tonnies amplifier), bandpass filtered (3 dB points at 8 Hz (24dB/octave) and 400 Hz (48 dB/octave)), and digitized at a sample rate of 1,024 per second. Samples of 256 points (250 ms) were taken 100 ms after the detection of a QRS complex (18).

- Fatiguing experiment

After measuring PI_{max}, the patients were instructed to make static inspiratory manoeuvres into an occluded mouthpiece. A small leak prevented the patients from using their buccal muscles to generate negative pressures. During these manoeuvres the patients had to keep their mouth pressure at 70 per cent of their PI_{max} (the target pressure). The patients could control the generated mouth pressure by a visual feedback system. The duration of an inspiratory manoeuvre was eight seconds, followed by a resting period of 22 seconds.
During each inspiratory manoeuvre, the mean value of three EMG-

samples after three consecutive QRS complexes was taken to calculate the centroid frequency (F_C) of the power spectrum of the diaphragm (F_CDIA) and the intercostal muscles (F_CIC) (19).
The fatiguing experiment was terminated when 1) the patient was too tired to generate the target pressure; 2) when the target pressure decreased more than 20 per cent during two consecutive inspiratory manoeuvres; or 3) when the duration of the experiment was ten minutes.
The results of the fatiguing experiment are presented as 1) the total duration of the inspiratory manoeuvres (T_{im}, seconds), and 2) the change of the F_CDIA and F_CIC during T_{im} (tgF_CDIA and tgF_CIC) (Hz/sec).

- Activities-in-Daily-Life (ADL) scores

Questionnaires about daily activities were filled in by the patients. The higher these scores (0 to 11), the better the patient could perform daily activities.

4-2.5. Data analysis

The baseline parameters of the two groups were compared by means of the Wilcoxon test. The changes during the training period within one group were also compared by the Wilcoxon test. Differences in response to treatment between the two groups were analysed by means of the Mann-Whitney U-test.

4-3. RESULTS

All selected patients completed the study. There were no significant differences between the two groups with regard to age, sex distribution, body measures and pulmonary function indices (Table 4-1).

	PR (n=20)	**PR+IMT** (n=20)
age, yr	60 (7)	58 (8)
sex, ♂:♀	16:4	14:6
height, m	171 (6)	171 (7)
FEV_1, L	1.56 (0.60)	1.42 (0.47)
FEV_1, %pred	51.7 (17.0)	46.9 (14.0)
FEV_1%IVC, %	44.6 (11.2)	42.5 (10.1)
FRC%TLC, %pred	115.1 (19.5)	127.0 (24.9)
TLC, %pred	99.5 (11.5)	103.7 (14.0)
K_{CO}, % pred	74.4 (21.7)	76.3 (19.1)
$compl_{ss}$, % pred	148.8 (73.2)	139.0 (31.6)

Table 4-1. Patient characteristics (means (SD)). PR: Pulmonary rehabilitation, IMT: Inspiratory muscle training.

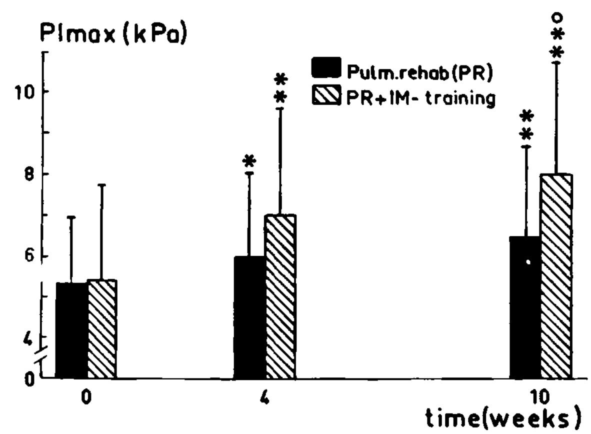

Figure 4-1. Maximal inspiratory mouth pressure (PI_{max}) during the training period in the PR group (filled bars) and in the PR+IMT group (hatched bars). * compared to baseline: $p<0.05$, ** $p<0.01$. O PR+IMT compared to PR: $p<0.001$.

After the training PI_{max} increased in both groups ($p<0.01$) (Figure 4-1). PI_{max} expressed as percentage of predicted increased in the PR group from 67.9 (22.8) (mean)(SD) to 81.9 (22.1) per cent, and in the PR+IMT group from 68.0 (26.6) to 100.8 (30.8) per cent. Additional TF-IMT resulted in a significant increase compared to the group without additional TF-IMT ($p<0.001$).
The endurance time (T_{im}) increased in both groups ($p<0.01$), but there were no significant differences between these increases (Figure 4-2).

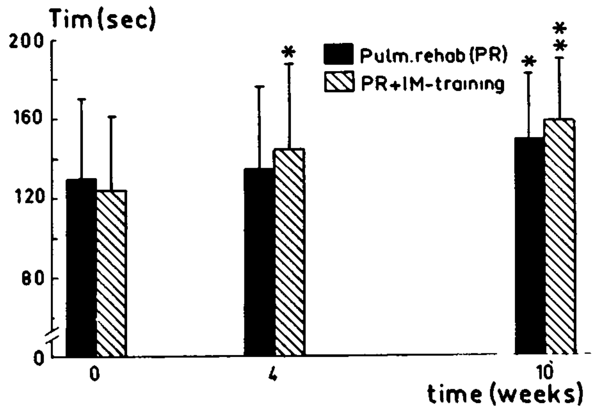

Figure 4-2. Endurance time (T_{im}) during the training period in the PR group (filled bars) and in the PR+IMT group (hatched bars). * compared to baseline: $p<0.05$, ** $p<0.01$.

EMG-fatigability of the diaphragm (TgF_cDIA) improved in both groups, but in the PR+IMT group this increase was more pronounced than in the PR group ($p<0.05$) (Figure 4-3). There was no change in EMG-fatigability of the intercostal muscles (tgF_cIC) in either of the groups (Figure 4-4).

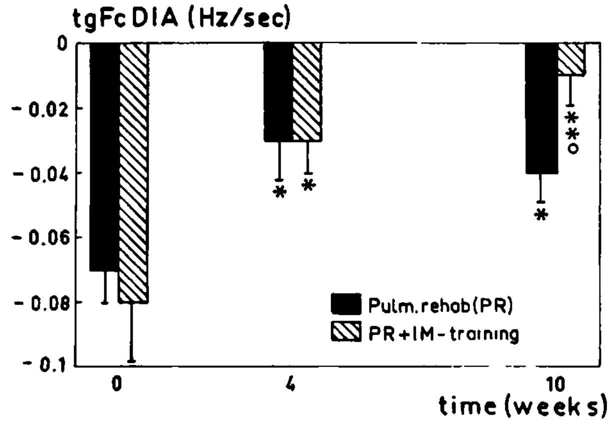

Figure 4-3. EMG-fatigability of the diaphragm (tgF_cDIA) during the training period in the PR group (filled bars) and in the PR+IMT group (hatched bars). * compared to baseline: $p<0.05$, ** $p<0.01$. O PR+IMT compared to PR: $p<0.05$.

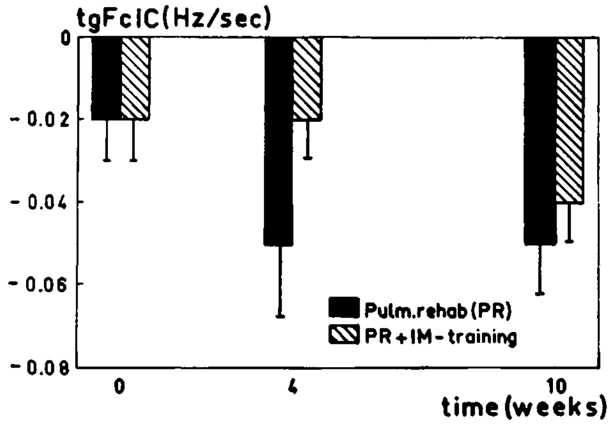

Figure 4-4. EMG-fatigability of the intercostal muscles (tgF_cIC) during the training period in the PR group (filled bars) and in the PR+IMT group (hatched bars).

	baseline	10 weeks	p-value
W_{max}, watt			
PR	97 (44)	127 (55)	<0.01
PR+IMT	93 (54)	116 (59)	<0.01
HR_{max}, beats/min			
PR	138 (16)	138 (17)	NS
PR+IMT	134 (19)	137 (24)	NS
$\dot{V}O_{2,max}$, L/min			
PR	1.46 (0.50)	1.62 (0.58)	<0.01
PR+IMT	1.37 (0.53)	1.47 (0.62)	<0.01
$\dot{V}CO_{2,max}$, L/min			
PR	1.48 (0.52)	1.71 (0.67)	<0.005
PR+IMT	1.46 (0.63)	1.55 (0.75)	<0.05
$\dot{V}E_{max}$, L/min			
PR	49.5 (15.6)	56.1 (18.8)	<0.01
PR+IMT	46.8 (19.6)	51.1 (21.3)	<0.01
BR, %			
PR	15.4 (26.1)	4.1 (20.9)	<0.01
PR+IMT	12.2 (20.7)	4.1 (19.3)	<0.01
▲ $PaCO_2$, kPa			
PR	0.78 (0.41)	0.84 (0.65)	NS
PR+IMT	0.77 (0.51)	0.73 (0.76)	NS

Table 4-2. Maximal bicycle ergometer test before and after training (means (SD)). PR: Pulmonary rehabilitation. IMT: Inspiratory muscle training. BR: breathing reserve, $(MVV-\dot{V}E_{max})/MVV$. ▲ $PaCO_2$: $PaCO_2$ at maximal exercise minus at rest.

The data of the exercise tests before and after the training period are summarized in Table 4-2. In both groups, maximal work load, $\dot{V}O_2$ and $\dot{V}CO_2$ at maximal exercise, and $\dot{V}E_{max}$ increased significantly. The heart rate at maximal exercise remained unchanged during the training period. As a consequence of the increased $\dot{V}E_{max}$, the breathing reserve (BR) decreased in both groups. For all these changes, there were no significant differences between the two groups.

The increase in the $PaCO_2$ during the exercise test did not change after the training period (Table 4-2).

The twelve-minute walking distance improved significantly in both groups, but relatively more in the PR+IMT group than in the PR group (Figure 4-5).

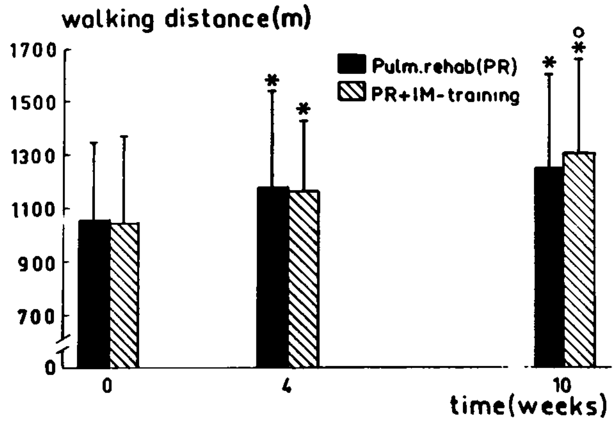

Figure 4-5. Twelve-minute walking distance during the training period in the PR group (filled bars) and in the PR+IMT group (hatched bars). * compared to baseline: $p<0.01$. O PR+IMT compared to PR: $p<0.05$.

	baseline	4 weeks	10 weeks
ADL scores			
PR	6.3 (2.3)	6.9 (2.3)	7.7 (2.3)**
PR+IMT	6.2 (2.4)	7.2 (2.3)*	8.4 (2.2)**

Table 4-3. Activities-in-Daily-Life (ADL) scores before and after the training period (means (SD)). Compared to baseline: * $p<0.05$, ** $p<0.01$.

ADL scores increased in both groups to the same extent (Table 4-3), without significant differences between the two groups.

4-4. DISCUSSION

The performance of the inspiratory muscles and the general exercise capacity in these COPD patients with a ventilatory limitation increased significantly in both the PR and the PR+IMT group. However, additional TF-IMT resulted in a greater improvement in strength and endurance of the inspiratory muscles, expressed in the increase in PI_{max} and the decrease in the EMG-fatigability of the diaphragm. Furthermore, the exercise endurance, as measured by means of the 12-min walking distance, was significantly better in the PR+IMT group.

The patients in this study were selected on the criterion of a normal resting arterial PCO_2 that increased during exercise. In these patients, the breathing reserve was abnormally low at maximal exercise, also indicating a ventilatory limitation. The performance of the inspiratory muscles in these patients may be one of the limiting factors of the exercise capacity. Therefore, these patients may be expected to benefit from IMT. Pardy (6,7) described a group of COPD patients with EMG-signs of fatigability of the inspiratory muscles during exercise. These patients showed a greater improvement of their exercise capacity after IMT than COPD patients without EMG-signs of fatigability during exercise. In other studies of the effects of IMT, however, patients were not selected on the cause of the exercise limitation. So, it is possible that IMT was applied to patients in whom inspiratory muscle performance was <u>not</u> the limiting factor of the exercise capacity.

The most effective method of IMT has not yet been established. Normocapnic hyperpnea has been shown to increase the endurance of the inspiratory muscles in patients with COPD (5). This resulted in an increase in the 12-min. walking distance and in arm and leg exercise. This training method, however, can only be applied in the laboratory, because of the necessary technical facilities.

Inspiratory resistive breathing has often been used to train the inspiratory muscles (2-4,6-10,20,21). In order to improve the performance of the inspiratory muscles, a target inspiratory flow or pressure has to be defined, as well as the duration of the inspiration and expiration (22). If these parameters are not defined, the patients can easily adopt a non-fatiguing breathing pattern with a low inspiratory flow rate. In that case the inspiratory muscles are not exposed to a considerable work load and will hardly be trained. This may contribute to the conflicting results of IMT. Recently, a pressure threshold device has been used by several investigators (3,20,23). In this way, a threshold inspiratory pressure has to be generated to create an inspiratory airflow. By using this device, Larson (3) showed a significant increase in the PI_{max} and in the 12-min. walking distance in a group of COPD patients who had trained their inspiratory muscles at 30 per cent of their PI_{max}.

It is not yet clear which target pressure, expressed as a percentage of PI_{max}, is the most effective. Some investigators used 30 (3), 50 (20) or 60 per cent (2) of PI_{max}. We used a target-pressure of 70 per cent of PI_{max}, which was fairly well tolerated by the patients.

The fatigability of the diaphragm was diminished in the PR as well as in the PR+IMT group, although significantly more in the latter group. It seems therefore that exercise as such may result in a training stimulus for the diaphragm. The fatigability of the intercostal muscles was not influenced by TF-IMT. This is not surprising, since the intercostal muscles operate near the optimum of their length-tension curve, which is enhanced by hyperinflation. So these muscles are likely to be well-trained. Indeed, Sanchez et al (24) showed that in COPD patients the intercostal muscles contained a higher activity of oxidative and glycolytic enzymes than in normal subjects. Therefore, IMT may be expected to have more effect on the diaphragm than on the intercostal muscles, which is supported by our findings.

One of the effects of IMT may be a reduced feeling of dyspnea during exercise. Besides the increase in strength and endurance of the inspiratory muscles, this reduced feeling of dyspnea may also contribute to an increased general exercise performance.

In conclusion, adding target-flow inspiratory muscle training to a pulmonary rehabilitation program in COPD patients with a ventilatory limitation, results in significantly more improvement of the strength of the inspiratory muscles and the EMG-fatigability of the diaphragm as well as in the exercise endurance of these patients, than PR alone. This has a beneficial effect on the twelve-minute walking distance.

4-5. SUMMARY

The effects of additional target-flow inspiratory muscle training (TF-IMT) on the performance of the inspiratory muscles and the general exercise capacity during a pulmonary rehabilitation program (PR) were studied in 40 COPD patients with a ventilatory limitation during exercise. All patients participated in a ten-week PR program. They were randomised to either receive additional TF-IMT (PR+IMT) or not (PR). TF-IMT was performed by means of a target-flow resistive device; the generated mouth pressure and the duration of inspiration and of the respiratory cycle were determined. The mean age of the patients was 59, the mean FEV_1 was approximately 50 per cent of predicted. After the training period maximal inspiratory mouth pressure and EMG-fatigability of the diaphragm were significantly better in the PR+IMT group than in the PR group. Maximal work load and ventilation at maximal exercise increased to the same extent in both groups. The twelve-minute walking distance also increased in both groups, but significantly more in the PR+IMT group than in the PR group.
It is concluded that additional TF-IMT during PR in COPD patients with a ventilatory limitation has an extra beneficial effect on the performance of the inspiratory muscles and on the exercise endurance.

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TARGET-FLOW INSPIRATORY MUSCLE TRAINING AT HOME AND DURING PULMONARY REHABILITATION IN COPD PATIENTS WITH A VENTILATORY LIMITATION DURING EXERCISE

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5-1. INTRODUCTION

Inspiratory muscle training (IMT) has been applied to patients with COPD to increase the strength and endurance of these muscles (1-9). The effects of IMT on the exercise capacity of patients with COPD are controversial. This may be caused by an inappropriate selection of patients who underwent IMT or by the method of IMT. Furthermore, the effects of additional IMT during a pulmonary rehabilitation (PR) program have not yet been studied.

The aim of this study is to compare the effects of an IMT program at home to IMT during pulmonary rehabilitation in a group of COPD patients with a ventilatory limitation of the exercise capacity, in terms of performance of the inspiratory muscles and general exercise capacity.

5-2. METHODS

5-2.1. Design of the study

Twenty COPD patients with a ventilatory limitation of their exercise capacity participated in a ten-week PR program with additional IMT. Another twenty patients started with (isolated) IMT at home. The patients were placed in the IMT group or in the PR+IMT group depending on the ability of the patients to visit the outpatient clinic daily.

Measurements of inspiratory muscle performance and exercise capacity were made before entering the program and after four and ten weeks. Informed consent was obtained from all patients.

5-2.2. Patients

Forty patients with COPD were selected from the outpatient clinic. In all of them a ventilatory limitation of their exercise capacity was established by means of a maximal incremental bicycle ergometer test. The ventilatory limitation was defined by a normal arterial PCO_2 at rest, which rose during progressive exercise. This may indicate an insufficiency of the inspiratory muscles to maintain an adequate alveolar ventilation during the higher metabolic rate of exercise.

5-2.3. Target-flow inspiratory muscle training

An incentive flowmeter (Inspirx, Intertech Resources Inc.) with an added resistance was used for target-flow IMT (TF-IMT). The patients were instructed to create an inspiratory flow rate at which the ball in the flowmeter reached the top of the device (the target-flow). The adjustable leak in the flowmeter was set by the physiotherapist so that the subject had to generate 70 per cent of his maximal inspiratory mouth pressure (PI_{max}) in order to keep the ball at the top of the flowmeter. The duration of the inspiration was set at three seconds by means of a metronome, the (unloaded) expiration at four seconds. TF-IMT was performed during fifteen minutes twice a day. In the patients who participated in the daily PR-program, TF-IMT was supervised by the physiotherapist once a day. Twice a week PI_{max} was measured and the target-flow was adjusted to the new PI_{max}. The home-IMT group visited the outpatient clinic once a week for supervision of the TF-IMT, measurement of PI_{max} and adjustment of the target-flow.

5-2.4. Pulmonary rehabilitation (PR) program

For a period of ten weeks the patients participated in the PR program, five days a week, two hours every day. The program consisted of exercise training, callisthenics, conventional physiotherapy and patient-education.

5-2.5. Measurements

- Maximal inspiratory mouth pressure (PI_{max})

PI_{max} was measured from residual volume (10). The highest value of four to seven maximal inspiratory manoeuvres was taken as PI_{max}.

- Electromyogram (EMG)

The diaphragmatic and intercostal EMG was recorded by surface electrodes (11). The EMG signals were filtered (8-400 Hz) and digitized (12).

- Fatiguing experiment

After measuring PI_{max}, the patients were instructed to make static inspiratory manoeuvres into an occluded mouthpiece. During these manoeuvres the patients had to keep their mouth pressure at 70 per cent of their PI_{max} (the target pressure). The patients could control the generated pressure by a visual feedback system. The duration of an inspiratory manoeuvre was eight seconds, followed by a period of rest of 22 seconds.
During each inspiratory manoeuvre, the centroid frequencies (F_c) of the power spectrum of the diaphragm (F_cDIA) and the intercostal muscles (F_cIC) were calculated (13).

The results of the fatiguing experiment are presented as 1) the total duration of the fatiguing inspiratory manoeuvres (T_{im}, seconds), and 2) the change of the F_cDIA and F_cIC during the experiment, in this study presented as tg F_cDIA/T_{im} and tg F_cIC/T_{im} (abbreviated as tgF_cDIA and tgF_cIC).

- Bicycle ergometer test

A maximal incremental exercise test to exhaustion was performed on a bicycle ergometer (Lode). Arterial blood samples were taken every three minutes for blood gas analysis (Ciba Corning 178 DMS). Minute ventilation ($\dot{V}E$), O_2-uptake ($\dot{V}O_2$) and CO_2-output ($\dot{V}CO_2$) were measured every 30 seconds (Oxycon IV, Mijnhardt).

- Twelve-minute walking distance

The patients were instructed to walk indoors as far as possible during twelve minutes (14). They were continuously encouraged in order to reach a maximal walking distance.

- Activities-in-Daily-Life (ADL) scores

Questionnaires about daily activities were filled in by the patients. The higher these scores (0 to 11), the better the patient was able to perform daily activities.

5-2.6. Data analysis

The baseline parameters of the two groups and the changes during the training period within one group were compared by the Wilcoxon test. Differences in response to treatment between the two groups were analysed by the Mann-Whitney U-test.

5-3. RESULTS

All selected patients completed the study. There were no significant differences between the two groups with regard to age, sex and pulmonary function data (Table 5-1).

PI_{max} increased significantly in both groups after the training (Figure 5-1). PI_{max} (kPa, mean (SD)) increased in the IMT group from initial 5.9(1.7) to 7.2(1.8) after four weeks and to 7.9 (2.3) after ten weeks. In the PR+IMT group PI_{max} increased from 5.4(2.4) to 7.0(2.5) after four weeks and to 8.0(2.8) after ten weeks. There were no significant differences between the groups.

	IMT (n=20)	PR+IMT (n=20)
age, yr	60 (8)	58 (8)
sex, ♂:♀	15:5	14:6
FEV_1, L	1.46 (0.47)	1.42 (0.47)
FEV_1, %pred	48.6 (14.4)	46.9 (14.0)
FEV_1%IVC	39.0 (10.4)	42.5 (10.1)
FRC%TLC, %pred	134.6 (20.0)	127.0 (24.9)
TLC, %pred	113.8 (13.2)	103.7 (14.0)
K_{CO}, % pred	72.2 (18.9)	76.3 (19.1)
$compl_{ss}$, % pred	139.0 (36.8)	139.0 (31.6)

Table 5-1. Patient characteristics (means (SD)). IMT: Inspiratory muscle training, PR: Pulmonary rehabilitation.

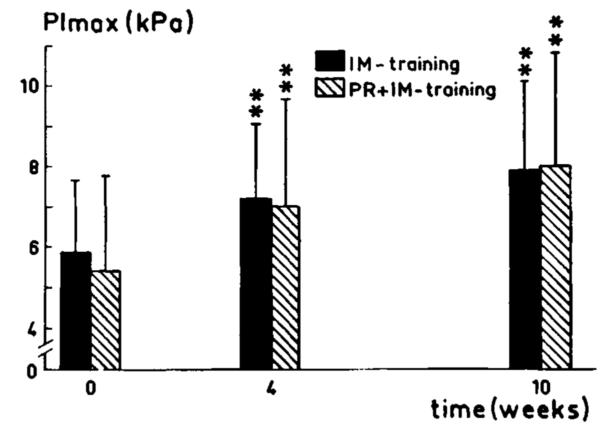

Figure 5-1. Maximal inspiratory mouth pressure (PI_{max}) during the training period in the IMT group (filled bars) and in the PR+IMT group (hatched bars). Data compared to baseline: * $p<0.05$, ** $p<0.01$.

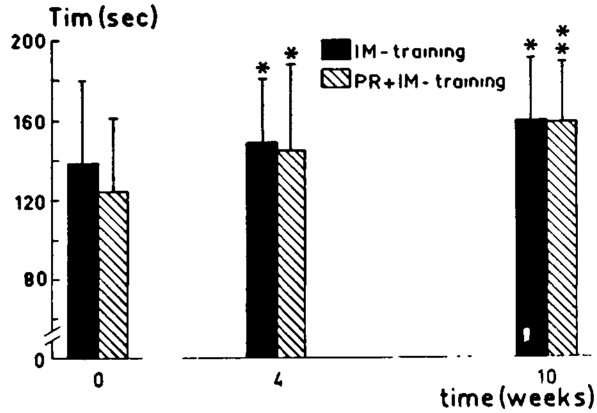

Figure 5-2. Endurance time (Tim) during the training period in the IMT group (filled bars) and in the PR+IMT group (hatched bars).

The endurance time (T_{im}) (Figure 5-2) increased in both groups with no significant differences between the two groups: in the IMT group from 138 (41) seconds to 149 (31) after four weeks and to 159 (30) after ten weeks; in the PR+IMT group from 124 (37) to 145 (41) after four weeks and to 158 (29) after ten weeks.
EMG-fatigability of the diaphragm (Figure 5-3) decreased significantly in the PR+IMT group, but not in the IMT group. There were no significant differences between the two groups. There was no change in EMG-fatigability of the intercostals in both groups (Figure 5-4).
In the IMT group, maximal work load (W_{max}), $\dot{V}O_2$ at maximal exercise and $\dot{V}E_{max}$ did not change during the training period (Table 5-2). Heart rate at W_{max} (HR_{max}) increased in the IMT group after the training period, suggesting the possibility of a higher effort without a real training effect. In the PR+IMT group, W_{max}, $\dot{V}O_{2,max}$ and $\dot{V}E_{max}$ were increased significantly after the training period. In the PR+IMT group HR_{max} did not change, indicating a real training effect. There were no significant differences between the two groups for all these parameters.

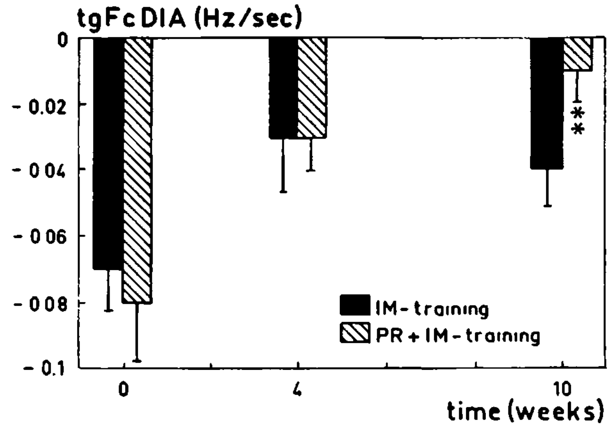

Figure 5-3. EMG-fatigability of the diaphragm (tgF_CDIA) during the training period in the IMT group (filled bars) and in the PR+IMT group (hatched bars). Data compared to baseline: ** $p<0.01$.

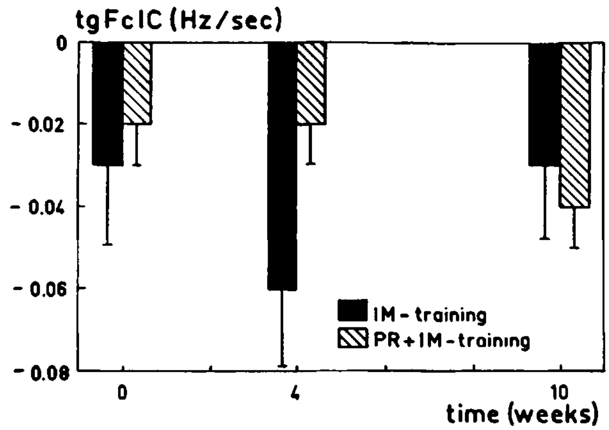

Figure 5-4. EMG-fatigability of the intercostal muscles (tgF_CIC) during the training period in the IMT group (filled bars) and in the PR+IMT group (hatched bars).

	baseline	10 weeks	p-value
W_{max}, watt			
IMT	107 (44)	119 (36)	NS
PR+IMT	93 (54)	116 (59)	<0.01
HR_{max}, 1/min			
IMT	131 (17)	138 (17)	<0.05
PR+IMT	134 (19)	137 (24)	NS
$\dot{V}O_{2,max}$, L/min			
IMT	1.47 (0.37)	1.54 (0.33)	NS
PR+IMT	1.37 (0.53)	1.47 (0.62)	<0.01
$\dot{V}E_{max}$, L/min			
IMT	49.6 (16.0)	51.9 (13.8)	NS
PR+IMT	46.8 (19.6)	51.1 (21.3)	<0.01
$\dot{V}E_{max}$/MVV, %			
IMT	90.6 (20.5)	94.8 (18.1)	NS
PR+IMT	87.9 (22.1)	96.0 (24.1)	<0.01
Walking distance, m			
IMT	1065 (248)	1207 (243)	<0.01
PR+IMT	1046 (323)	1309 (376)	<0.01*

Table 5-2. Indices of the exercise capacity before and after the training period in the IMT group and the PR+IMT group. Values are means (SD). NS: not significantly different from baseline value. * PR+IMT compared to IMT: p<0.001 (Mann-Whitney U-test).

The twelve-minute walking distance (Table 5-2) improved in both groups, but significantly more in the PR+IMT group than in the IMT group (p<0.001).

ADL scores increased in the PR+IMT group from 6.2(2.4) to 8.4(2.2) (p<0.01), but did not change in the IMT group (initial 6.4(2.0), after ten weeks 6.3(1.3) (NS)). These changes were also significantly more pronounced in the PR+IMT group than in the IMT group (p<0.001).

5-4. DISCUSSION

The patients in this study were selected on the criterion of a normal arterial PCO_2 at rest that increased during exercise. The performance of the inspiratory muscles in these patients may contribute to the limitation of the exercise capacity. Therefore, patients selected on this criterion may be expected to benefit from IMT. In most reported studies of the effects of IMT, however, patients were not selected on the account of the cause of their exercise limitation (1-9) and this may explain the conflicting results of IMT.

Inspiratory resistive breathing has often been used to train the inspiratory muscles. In order to train the inspiratory muscles effectively, a target inspiratory flow or pressure has to be defined, as well as the duration of the inspiration and expiration (15). If these parameters are not defined, the patients can easily adopt a non-fatiguing breathing pattern with a low inspiratory flow rate. This might be especially the case when IMT is performed at home without regular supervision. In our study the patients were frequently supervised while performing IMT, especially the PR+IMT group. The most effective target inspiratory pressure expressed as a percentage of PI_{max} has not yet been defined. Some investigators used 30 per cent (9), 50 per cent (16) or 60 per cent (6) of PI_{max}. Our patients trained at a percentage of 70 per cent of PI_{max}, which was well tolerated.

EMG-fatigability of the diaphragm was significantly diminished in the PR+IMT group but not in the IMT group. The fatigability of the intercostal muscles was not significantly changed by IMT in either group. This is in line with expectations based on the length-tension relationships of the inspiratory muscles, as well as the biochemical findings of Sanchez et al (17).

$\dot{V}E_{max}$ after the training period was closer to the predicted maximal ventilation ($37.5xFEV_1$) (18) than before training. This indicates a better performance of the inspiratory muscles. Inspiratory muscle strength improved in the IMT and the PR+IMT group to the same extent. The general exercise capacity, however, increased significantly only in the PR+IMT group and not in the

IMT group, except for the walking distance. ADL scores and the walking distance showed a significantly greater increase in the PR+IMT group than in the IMT group.

It is concluded that inspiratory muscle training is effective in COPD patients who were selected on the criterion of a ventilatory limitation. Inspiratory muscle training during pulmonary rehabilitation has a substantial better effect on the patients' performance than isolated inspiratory muscle training.

5-5. SUMMARY

The effects of a ten-week inspiratory muscle training program (IMT) at home were compared to IMT during a ten-week pulmonary rehabilitation program (PR) in 40 COPD patients with a ventilatory limitation of the exercise capacity. IMT was performed with a target-flow resistive device; the generated mouth pressure as well as the duty cycle were imposed. The mean age of the patients was 59, the mean FEV_1 was 48 per cent of predicted. In the training period inspiratory muscle strength improved in both groups to the same degree. EMG-fatigability of the diaphragm improved in the PR+IMT group, but not in the IMT group. In the <u>IMT group</u>, the 12-min. walking distance was increased after the training period, but maximal work load (W_{max}), $\dot{V}O_{2,max}$ and ADL scores were not change. In the <u>PR+IMT group</u>, however, W_{max}, $\dot{V}O_{2,max}$, walking distance and ADL scores were improved significantly after the training period. Walking distance and ADL scores showed a greater improvement in the PR+IMT group than in the IMT group. It is concluded that both isolated IMT and PR+IMT in COPD patients with a ventilatory limitation have a beneficial effect on the performance of the inspiratory muscles, but PR+IMT results in a significantly greater improvement of the exercise capacity than IMT alone.

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CHAPTER 6

LONG-TERM EFFECTS OF TARGET-FLOW INSPIRATORY MUSCLE TRAINING AND PULMONARY REHABILITATION IN COPD PATIENTS WITH A VENTILATORY LIMITATION DURING EXERCISE

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Submitted for publication

6-1. INTRODUCTION

Fatigability of the inspiratory muscles may limit the exercise capacity of patients with chronic obstructive pulmonary disease (COPD) (1). Inspiratory muscle training (IMT) can improve strength and endurance of these muscles (2-10). Also the physical exercise capacity may improve (2,4-6,10), but this was not the case in all studies (8,9).
In a previous study we investigated the effects of pulmonary rehabilitation (PR) with or without additional IMT in a group of COPD patients with a ventilatory limitation of their exercise capacity, i.e. a rising arterial PCO_2 during exercise (11,12). The combined training program (PR+IMT) resulted in a significantly greater improvement of the maximal inspiratory mouth pressure (PI_{max}), of the electromyographic fatigability of the diaphragm and of the twelve-minute walking distance, than PR alone. An isolated IMT program at home had no effects on the maximal exercise capacity.
It is not known how long short-term effects on the performance of the inspiratory muscles and the physical exercise capacity persist after the training period. The aim of this study is, therefore, to measure the long-term effects during a one-year follow-up period of a PR program, an IMT program combined with a PR program and an IMT program alone in a group of COPD patients with a ventilatory limitation during exercise.

6-2. METHODS

6-2.1. Design of the study

Sixty COPD patients with a ventilatory limitation of their exercise capacity participated in a ten-week training program. They were placed in one of three treatment groups: a group with a PR program, a group with an IMT program, or a group with a combination of these two treatments (PR+IMT). Inspiratory muscle performance and physical exercise capacity were measured before entering the program, during the training period and at three, six and twelve months after the training period. Informed consent was obtained from all patients.

6-2.2. Patients

Patients with COPD were selected from the outpatient clinic. All patients had moderate to severe airflow obstruction without significant changes after inhalation of bronchodilators. The characteristics of the patients are shown in Table 6-1.
A ventilatory limitation of the exercise capacity was established in all patients by means of a maximal bicycle ergometer test. The ventilatory limitation was defined as a normal arterial PCO_2 at rest that rose during progressive exercise. This may indicate an insufficiency of the inspiratory muscles to maintain an adequate alveolar ventilation during exercise. The ventilation at maximal exercise ($\dot{V}E_{max}$) was close to the predicted maximal voluntary ventilation (MVV, 37.5xFEV_1) (13), emphasizing the ventilatory limitation. The alveolar-arterial oxygen difference ($D(A-a)O_2$) did not increase by more than 2 kPa at maximal exercise, so a diffusion disorder was excluded (14).

6-2.3. Training

- Grouping of the patients

Forty patients participated in the PR program. Before entering, these patients were randomized to receive additional IMT or not (PR group and PR+IMT group). Another twenty patients only performed IMT at home (IMT group). These patients were not able to visit the outpatient clinic daily because of geographic or transport problems.

- Pulmonary rehabilitation program

This was a ten-week training program, five days a week, two hours every day. It consisted of callisthenics, exercise training (cycling, walking, training of back, shoulder and abdominal muscles), conventional physiotherapy (breathing retraining, relaxation exercises) and education about the pulmonary disease and the purpose and use of the medications.

- Target-flow inspiratory muscle training (TF-IMT)

An incentive flowmeter (Inspirx, Intertech Resources Inc.) with an added resistance was used for TF-IMT. The patients were instructed to generate an inspiratory flow rate at which the ball in the flowmeter reached the top of the device (the target-flow). The adjustable leak in the flowmeter was set by the physiotherapist, so that the patient had to generate 70 per cent of his maximal inspiratory mouth pressure (PI_{max}) in order to keep the ball at the top of the flowmeter. The duration of the inspiration was set at three seconds by using a metronome, the (un-loaded) expiration at four seconds. The patients performed TF-IMT during fifteen minutes twice a day, supervised by the physiotherapist.

Twice a week PI_{max} was measured and the target-flow was adjusted to the new PI_{max}. The patients who performed the IMT-program at home, visited the investigator every week for supervision of the IMT, measurement of PI_{max} and adjustment of the target-flow.

- Follow-up period

The patients were encouraged to continue performing physical exercises after the training period. They could continue training the inspiratory muscles if they wanted.

6-2.4. Measurements

- Lung function

Spirometry was performed by means of a wet spirometer (Pulmonet III, Gould-Godart). Total lung capacity (TLC) was measured by the closed circuit helium-dilution method (Pulmonet III). The diffusion capacity (K_{CO}) was measured by using the single breath-holding carbon monoxide method (Morgan). Predicted values were derived from Quanjer (15).

- Maximal inspiratory mouth pressure (PI_{max})

PI_{max} from residual volume (RV) was measured by using a flanged occluded mouthpiece with a small leak, connected to a manometer (Validyne). The highest value of four to seven maximal inspiratory manoeuvres was taken as PI_{max}.

- Electromyogram (EMG)

The diaphragmatic and intercostal EMG was recorded by surface electrodes (16). For the diaphragm, the electrodes were placed in the 6th and 7th intercostal spaces on the right anterior axillary line (16). The intercostal electrodes were placed in the 2nd and 3rd left intercostal spaces, 2 cm from the edge of the sternum. The EMG signals were filtered (8-400 Hz) and digitized (17).

- Fatiguing experiment

After measuring PI_{max}, the patients were instructed to make static inspiratory manoeuvres into an occluded mouthpiece. A small leak prevented the patients from using their buccal muscles to generate negative pressures. During these manoeuvres the patients had to keep their mouth pressure at 70 per cent of their PI_{max} (the target pressure). The patients could control the generated mouth pressure by a visual feedback system. The duration of an inspiratory manoeuvre was eight seconds, followed by a period of rest of 22 seconds.
During each inspiratory manoeuvre, the centroid frequencies (F_c) of the power spectrum of the diaphragm (F_cDIA) and the intercostal muscles (F_cIC) were calculated (18).
The results of the fatiguing experiment are presented as 1) the total duration of the fatiguing inspiratory manoeuvres (T_{im}, seconds), and 2) the change of the F_cDIA and F_cIC during the

experiment, in this study presented as tg F_cDIA/T_{im} and tg F_cIC/T_{im} (abbreviated as tgF_cDIA and tgF_cIC).

- Bicycle ergometer test

A maximal incremental exercise test was performed on an electrically braked bicycle ergometer (Lode). An estimation of the maximal work load (W_{max} pred, watts) was made by the equation: 1.7 x weight(kg) + 40 x FEV_1(L) -25 (19).
Every minute the work load was increased by ten per cent of W_{max} pred. Arterial blood samples were taken every three minutes for blood gas analysis (Ciba Corning 178 DMS). Minute ventilation ($\dot{V}E$), O_2-uptake ($\dot{V}O_2$) and CO_2-output ($\dot{V}CO_2$) were measured every 30 seconds (Oxycon IV, Mijnhardt).

- Twelve-minute walking distance

The patients were instructed to walk indoors as far as possible during twelve minutes (20). They were continuously encouraged in order to reach a maximal walking distance. Before entering the study, they had one training session to become familiar with the test.

- Activities-in-Daily-Life scores (ADL)

Questionnaires about daily activities were filled in by the patients. The higher these scores (0 to 11), the better the patient was able to perform daily activities.

6-2.5. Data analysis

The baseline parameters of the three groups were compared by means of the Wilcoxon test. The changes during the training period within one group were also compared by the Wilcoxon test. Differences in response to treatment between the two groups were analysed by the Mann-Whitney U-test. A Spearman correlation test was used to detect significant correlations between the parameters, tested.

6-3. RESULTS

There were no significant differences between the three treatment groups with regard to age, sex distribution and lung function indices (Table 6-1).

	PR (n=20)		PR+IMT (n=20)		IMT (n=20)	
age, yr	60	(7)	58	(8)	60	(8)
sex, ♂:♀	16:4		14:6		15:5	
FEV_1, L	1.56	(0.60)	1.42	(0.47)	1.46	(0.47)
FEV_1, %pred	51.7	(16.7)	46.9	(14.0)	48.6	(14.4)
FEV_1%IVC	44.6	(11.2)	42.5	(10.1)	39.0	(10.4)
TLC, %pred	99.5	(11.5)	103.7	(14.0)	113.8	(13.2)
K_{CO}, % pred	74.4	(21.7)	76.3	(19.1)	72.2	(18.9)

Table 6-1. Age, sex distribution and lung function data in the patient groups. PR: Pulmonary rehabilitation; IMT: Inspiratory muscle training. Values are means (SD).

All selected patients completed the training period. Ten patients (four in the PR group, three in the PR+IMT group and three in the IMT group) did not complete the follow-up period. In three of these patients angina pectoris developed; in two patients a pulmonary malignancy was discovered and five patients were not able to visit the clinic for geographic reasons.

There were no changes in the lung function tests during the study period.

During the ten-week training period PI_{max} increased in all groups ($p<0.01$) (Figure 6-1). IMT alone or in combination with PR resulted in a significantly greater increase, as compared to the group without additional IMT ($p<0.001$). During the follow-up period there was a slow decrease in PI_{max} but it still remained above the baseline values in all groups.

EMG-fatigability of the diaphragm (tgF_cDIA) decreased after the training period in the PR and in the PR+IMT group, but in the PR+IMT group this decrease was more pronounced than in the PR group ($p<0.05$) (Figure 6-2). There was, however, a gradual increase in the diaphragm fatigability during the follow-up period, so that the values at three, six and twelve months were not significantly different from the initial values any more.

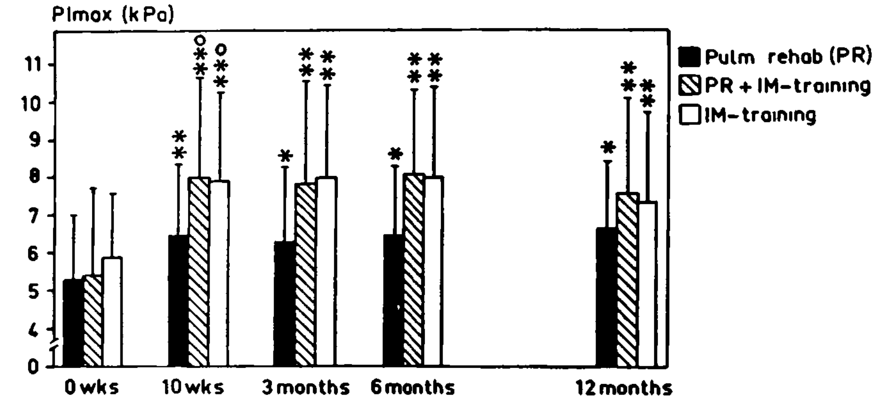

Figure 6-1. Long-term effects of the ten-week training period on maximal inspiratory mouth pressure (PI_{max}) in the PR group (filled bars), in the PR+IMT group (hatched bars) and in the IMT group (open bars). * compared to baseline: p<0.05, ** p<0.01. O PR+IMT compared to PR: p<0.001; IMT compared to PR: p<0.001.

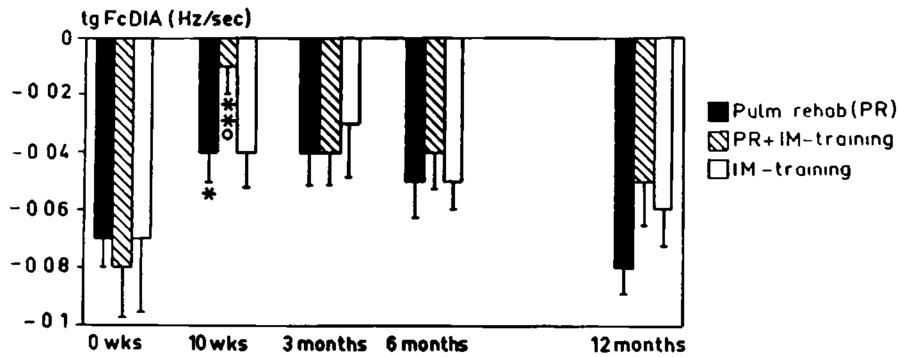

Figure 6-2. Changes in the EMG-fatigability of the diaphragm (tgF_cDIA) during the training period and after one year in the PR group (filled bars), in the PR+IMT group (hatched bars) and in the IMT group (open bars). * compared to baseline: p<0.05, ** p<0.01. O PR+IMT compared to PR: p<0.05.

There were no changes in EMG-fatigability of the intercostal muscles (tgF_CIC) in the three groups during and after the training period. There were no significant correlations between baseline (or changes in) PI_{max} and baseline (or changes in) tgF_CDIA or tgF_CIC.
After the training period maximal work load (W_{max}), $\dot{V}O_2$ at maximal exercise and $\dot{V}E_{max}$ increased significantly in the PR and the PR+IMT group, but not in the IMT group (Table 6-2). After one year W_{max} was only significantly above the baseline value in the PR group. $\dot{V}O_{2,max}$ and $\dot{V}E_{max}$ were no longer significantly different from baseline values in the three groups. For all these changes, there were no significant differences between the groups.
The twelve-minute walking distance (Table 6-2) improved in all groups after the training period, but significantly more in the PR+IMT group than in the PR group or the IMT group ($p<0.05$). In the follow-up period the walking distance remained significantly above the baseline values, but the differences between the three groups disappeared.
Baseline twelve-minute walking distance was correlated with baseline W_{max} ($R=0.73$, $p<0.0001$). Baseline PI_{max} was correlated with both walking distance ($R=0.39$, $p<0.005$) and with W_{max} at the start of the study ($R=0.39$, $p<0.005$).
ADL scores increased in the PR and the PR+IMT group to the same extent (Table 6-2), but decreased after one year. Isolated IMT did not influence the ADL scores. Baseline ADL scores were correlated with baseline walking distance ($R=0.43$, $p<0.001$). Also, the change in the ADL scores after the training period was correlated with the change in the walking distance after the training period ($R=0.26$, $p<0.05$). During the one-year follow-up period there were no significant correlations between these parameters.

	baseline	10 weeks	1 year
W_{max}, watt			
PR	97 (44)	127 (55)**	114 (49)*
PR+IMT	93 (54)	116 (59)**	104 (48)
IMT	107 (44)	119 (36)	113 (39)
HR_{max}, beats/min			
PR	138 (16)	138 (17)	141 (15)
PR+IMT	134 (19)	137 (24)	142 (22)*
IMT	131 (17)	138 (17)*	134 (20)
$\dot{V}O_{2,max}$, L/min			
PR	1.46 (0.50)	1.62 (0.58)**	1.50 (0.49)
PR+IMT	1.37 (0.53)	1.47 (0.62)**	1.49 (0.48)
IMT	1.47 (0.37)	1.54 (0.33)	1.33 (0.31)
$\dot{V}E_{max}$, L/min			
PR	49.5 (15.6)	56.1 (18.8)**	52.5 (21.1)
PR+IMT	46.8 (19.6)	51.1 (21.3)**	52.0 (19.7)
IMT	49.6 (16.0)	51.9 (13.8)	49.7 (16.5)
Walking distance, m			
PR	1057 (284)	1251 (354)**	1222 (321)**
PR+IMT	1046 (323)	1309 (376)**O	1262 (368)**
IMT	1065 (248)	1207 (243)**	1191 (278)*
ADL scores			
PR	6.3 (2.3)	7.7 (2.3)**#	7.4 (2.4)
PR+IMT	6.2 (2.4)	8.4 (2.2)**#	7.0 (2.4)
IMT	6.4 (2.0)	6.3 (1.6)	6.3 (1.9)

Table 6-2. Results of exercise tests and ADL scores before and after the ten-week training period and after a one-year follow-up in the three groups. PR: Pulmonary rehabilitation; IMT: Inspiratory muscle training. Values are means (SD). Data compared to baseline: * $p<0.05$; ** $p<0.01$. Data compared to PR and IMT: O $p<0.05$. Data compared to IMT: # $p<0.001$.

6-4. DISCUSSION

Inspiratory muscle **strength** remained above the baseline values during the follow-up period. The initial improvement of the **endurance** of the diaphragm, as measured from the decrease in the EMG-fatigability in the PR and the PR+IMT group, disappeared during the follow-up period. W_{max} and the twelve-minute walking distance increased after the training period in the PR and the PR+IMT group, and were still significantly higher than baseline values after one year, except for W_{max} in the PR+IMT group. The same pattern was seen in the twelve-minute walking distance in the IMT group.

The patients in this study were selected on the criterion of a normal arterial PCO_2 at rest that increased during exercise. The performance of the inspiratory muscles in these patients may be one of the limiting factors of the exercise capacity. Therefore, these patients may be expected to benefit from IMT.

In order to train the inspiratory muscles effectively, a target inspiratory flow or pressure has to be defined, as well as the duration of the inspiration and expiration (21). If these parameters are not defined, the patients may easily adopt a non-fatiguing breathing pattern with a low inspiratory flow rate during IMT. This might be especially the case when patients perform IMT at home without regular supervision.

After one year, inspiratory muscle strength and physical exercise capacity were still increased compared to baseline values. Presumably this is caused by the continued physical activities after the training period. Moreover, about 70 per cent of the patients who had performed IMT, continued IMT once daily, indicating a subjective beneficial experience of IMT. To our knowledge, no studies have been published about the long-term effects of PR or IMT with regard to the performance of the inspiratory muscles or the physical exercise performance.

ADL scores and the twelve-minute walking distance are indicators of the **endurance** capacity of the patients and were correlated with each other in the training period. PI_{max} and W_{max} (reflecting the **strength** of the patients) were also correlated.

The walking distance, however, was also correlated with W_{max}, emphasizing the relationship between endurance and strength in the patients. The disappearence of these correlations during the follow-up period may be explained by the fact that changes in these parameters are influenced by factors like motivation and type and intensity of exercises after the training period.
It is concluded that inspiratory muscle training and pulmonary rehabilitation are effective in COPD patients with a ventilatory limitation. During one year after the training period inspiratory muscle strength and the physical exercise capacity remain above the baseline values. Continuation of the physical activities is essential in order to retain the improved exercise capacity after the training period.

6-5. SUMMARY

The long-term effects of a ten-week pulmonary rehabilitation program (PR) were compared with an inspiratory muscle training program (IMT) at home and to IMT during a PR program (PR+IMT) in 60 COPD patients with a ventilatory limitation during exercise (mean age ±59, mean FEV_1 ±50 per cent of predicted). Inspiratory muscle strength and the twelve-minute walking distance improved in all groups in the training period and remained above the baseline values during a one-year follow-up period. EMG-fatigability of the diaphragm improved during the training period in both the PR and the PR+IMT group, but decreased in the follow-up period. Maximal work load and ADL scores increased during the training period in the PR and the PR+IMT group, but these improvements had disappeared after one year. These results indicate that continuation of physical exercise after a training program is important in order to maintain an improved physical condition.

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CHAPTER 7

PSYCHOLOGICAL CHANGES DURING PULMONARY REHABILITATION AND TARGET-FLOW INSPIRATORY MUSCLE TRAINING IN COPD PATIENTS WITH A VENTILATORY LIMITATION DURING EXERCISE

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7-1. INTRODUCTION

In patients with chronic obstructive pulmonary disease (COPD) the physical exercise capacity is usually diminished. Weakness and fatigability of the inspiratory muscles during exercise may contribute to the limitation of the exercise capacity (1).
The impaired lung function and physical performance may lead to disabilities in daily life, in occupation and in recreation. In turn, this causes the impairment of frustration, depression and feelings of social inadequacy and of hostility. The vicious circle is completed by the mechanism that these psychological changes will lead to inactivity, detraining, increased dyspnea on exertion, anxiety and lowered mobility (2).
Pulmonary rehabilitation (PR) aims at optimal medical treatment of the disease and breaking the vicious circle by reconditioning the patients, encouraging them to perform optimally in spite of their impairment, and to restore their self-confidence.
The vicious circle as descibed above, suggests a correlation between the impairment of the physical performance of the patients and parameters that measure the psychological aspects described above.
The aims of this study are 1) to compare the acute and long-term effects of a PR program and a target-flow inspiratory muscle training (TF-IMT) program on psychological parameters in a group of COPD patients with a ventilatory limitation during exercise and 2) to investigate if psychological parameters have a predictive value on the effects of these training programs.

7-2. METHODS

7-2.1. Design of the study

Sixty COPD patients with a ventilatory limitation of their exercise capacity participated in a ten-week training program. They were placed in one of three treatment groups: a group with a PR program, a group with a TF-IMT program, or a group with a combination of these two treatments. Psychological parameters and exercise capacity were measured before and immediately after the training program and during one year after the training period.

7-2.2. Patients

Sixty patients with COPD and a ventilatory limitation during exercise were selected from the outpatient clinic. Patients with cardiovascular or neuromuscular problems were excluded from the study. All patients had moderate to severe airflow obstruction without significant changes after inhalation of bronchodilators. The characteristics of the patients are shown in Table 7-1.
A ventilatory limitation of the exercise capacity was established in all patients by means of an incremental maximal bicycle ergometer test. The ventilatory limitation was defined as a normal arterial PCO_2 at rest that rose during progressive exercise. This may indicate an insufficiency of the respiratory muscles to maintain an adequate alveolar ventilation during the higher metabolic rate of exercise.

7-2.3. Measurements

- Lung function

Total lung capacity (TLC) was measured by the closed circuit helium-dilution method (Pulmonet III, Gould-Godart). Spirometry was performed by means of a wet spirometer (Pulmonet III). The diffusion capacity (K_{CO}) was measured by the single breath-holding carbon monoxide method (Morgan). Predicted values were derived from Quanjer (3).

- Bicycle ergometer test

A maximal incremental exercise test until exhaustion was performed on an electrically braked bicycle ergometer (Lode). An estimation of the maximal work load (W_{max} pred, watts) was made by the equation: W_{max} pred=1.7 x weight(kg) +40 x FEV_1(L) -25 (4). Every minute the work load was increased by ten per cent of W_{max} pred.

- Twelve-minute walking distance

The patients were instructed to walk indoors as far as possible during twelve minutes (5). They were continuously encouraged in order to reach a maximal walking distance. Before entering the study, they had one training session to become familiar with the test.

- Activities-in-Daily-Life (ADL) scores

Questionnaires about daily activities were filled in by the patients. The higher these scores (0 to 11), the better the patient was able to perform daily activities (6).

- Psychological parameters

The patients completed 2 questionnaires:

1- the Symptom Checklist (SCL-90), comprising items related to anxiety, depression, hostility and physical complaints. The SCL-90 is validated; values for a normal population are available, with correction for sex (7);

2- the Dutch Personality Inventory (DPI), which includes items directed at general personality traits, like social inadequacy and self-esteem. These scores can be compared to values for a normal population, corrected for age, sex and level of education (8).

7-2.4. Training

- Grouping of the patients

Forty patients participated in the PR program. Before entering, these patients were randomized to receive additional TF-IMT or not (PR group and PR+IMT group). Another twenty patients only performed TF-IMT at home. These patients were not able to visit the outpatient clinic daily because of geographic or transport problems (IMT group).

- Pulmonary rehabilitation program

This was a ten-week training program, five days a week, two hours every day. The program consisted of callisthenics, exercise training (cycling, walking, training of back, shoulder and abdominal muscles), conventional physiotherapy (breathing retraining, relaxation exercises), and education about the pulmonary disease and the purpose and use of the medications.

- Target-flow inspiratory muscle training

An incentive flowmeter (Inspirx, Intertech Resources Inc.) with an added resistance was used for TF-IMT. The patients were instructed to inspire during three seconds at a flow rate at which the ball in the flowmeter reached the top of the device (the target-flow), followed by an (unloaded) expiration of four seconds. The adjustable leak in the flowmeter was set at a level at which the patient had to generate 70 per cent of his maximal inspiratory mouth pressure (PI_{max}) in order to keep the ball at the top of the flowmeter. TF-IMT was performed during fifteen minutes twice a day, supervised by the physiotherapist. Twice a week PI_{max} was measured and the target-flow was adjusted to the new PI_{max}.

- **Follow-up period**

The patients were encouraged to continue performing physical exercises after the training period. They could continue training the inspiratory muscles if they wanted.

7-2.5. Data analysis

The baseline parameters of the three groups were compared by means of the Wilcoxon test. The changes during the training period within one group were compared by the Wilcoxon test. Differences in response to treatment between the two groups were analysed by the Mann-Whitney U-test. A Spearman correlation test was used to detect significant correlations between the tested parameters.

7-3. RESULTS

All patients completed the training period. There were no significant differences between the three groups with regard to age, sex distribution and pulmonary function indices (Table 7-1). Ten patients (four in the PR group, three in the PR+IMT group and three in the IMT group) did not complete the follow-up period. In three of these patients angina pectoris developed; in two patients a pulmonary malignancy was discovered and five patients were not able to visit the clinic for geographic reasons.

	PR (n=20)	**PR+IMT** (n=20)	**IMT** (n=20)
age, yr	60 (7)	58 (8)	60 (8)
sex, ♂:♀	16:4	14:6	15:5
FEV_1, L	1.56 (0.60)	1.42 (0.47)	1.46 (0.47)
FEV_1, %pred	51.7 (16.7)	46.9 (14.0)	48.6 (14.4)
FEV_1%IVC	44.6 (11.2)	42.5 (10.1)	39.0 (10.4)
TLC, %pred	99.5 (11.5)	103.7 (14.0)	113.8 (13.2)
K_{CO}, % pred	74.4 (21.7)	76.3 (19.1)	72.2 (18.9)

Table 7-1. Age, sex distribution and lung function data in the patient groups. PR: Pulmonary rehabilitation; IMT: Inspiratory muscle training. Values are means (SD).

	baseline		10 weeks		1 year	
W_{max}, watt						
PR	97	(44)	127	(55) **	114	(49) *
PR+IMT	93	(54)	116	(59) **	104	(48)
IMT	107	(44)	119	(36)	113	(39)
12-MWD, m						
PR	1057	(284)	1251	(354)**	1222	(321)**
PR+IMT	1046	(323)	1309	(376)**O	1262	(368)**
IMT	1065	(248)	1207	(243)**	1191	(278)*
ADL scores						
PR	6.3	(2.3)	7.7	(2.3)**#	7.4	(2.4)
PR+IMT	6.2	(2.4)	8.4	(2.2)**#	7.0	(2.4)
IMT	6.4	(2.0)	6.3	(1.6)	6.3	(1.9)

Table 7-2. Results of exercise tests and ADL scores before and after the ten-week training period and after a one-year follow-up in the three groups. PR: Pulmonary rehabilitation; IMT: Inspiratory muscle training. W_{max}: maximal work load; 12-MWD: twelve-minute walking distance; ADL: activities in daily life. Values are means (SD). Data compared to baseline: * $p<0.05$; ** $p<0.01$. Data compared to PR and IMT: O $p<0.05$. Data compared to IMT: # $p<0.001$.

Maximal work load (W_{max}) increased significantly in the PR and the PR+IMT group after the training period, but not in the IMT group (Table 7-2). After one year W_{max} was only significantly above the baseline value in the PR group. The twelve-minute walking distance (Table 7-2) improved in all groups after the training period, but there was a significantly greater improvement in the PR+IMT group than in the PR group or the IMT group. In the follow-up period the walking distance remained above the baseline values, but the differences between the three groups disappeared. ADL scores increased in the PR and the PR+IMT group to the same extent (Table 7-2), but decreased after one year. Isolated TF-IMT did not influence the ADL scores.

		baseline	10 weeks	1 year
Anxiety	**PR**	15.4 (4.9) O	12.8 (2.9) *	13.1 (3.3) *
(13.0, 10-50)	**PR+IMT**	17.5 (8.2) O	14.6 (6.4) *	17.2 (8.8) O
	IMT	16.0 (5.5) O	5.6 (6.5) O	15.3 (5.0) O
Depression	**PR**	24.7 (8.9) O	20.8 (5.0) *	20.6 (4.5) *
(20.0, 16-80)	**PR+IMT**	28.4 (11.5)O	24.4 (9.5) *	26.3 (11.3)O
	IMT	29.0 (12.1)O	26.9 (11.3)O	26.5 (10.3)O
Hostility	**PR**	8.6 (2.6)	7.0 (1.5)	7.0 (1.3)
(7.5, 6-30)	**PR+IMT**	8.6 (3.2)	7.1 (1.9)	8.3 (2.6)
	IMT	8.1 (2.9)	7.2 (1.7)	7.2 (1.8)
Physical	**PR**	21.1 (6.4) O	17.9 (3.7)	18.7 (4.0)
complaints	**PR+IMT**	23.1 (8.2) O	20.0 (7.1)	21.4 (7.9)
(16.6, 12-60)	**IMT**	23.0 (8.1) O	22.9 (8.1) O	22.4 (7.9) O
Social	**PR**	14.1 (7.8) O	9.2 (6.4)	9.5 (6.5)
inadequacy	**PR+IMT**	12.3 (9.6)	10.4 (8.5)	11.8 (9.9)
(9.5, 0-45)	**IMT**	9.5 (6.3)	9.3 (5.6)	9.1 (6.4)
Self-esteem	**PR**	25.0 (6.6) O	24.9 (5.9) O	24.2 (6.4) O
(28.0,0-57)	**PR+IMT**	23.6 (7.5) O	25.2 (7.4)	24.7 (6.8)
	IMT	24.9 (5.5) O	23.6 (6.4) O	23.7 (5.4) O

Table 7-3. Psychological parameters before and after the training period in the PR group, in the IMT group (IMT) and in the PR+IMT group. Data are means (SD). (): predicted value and range for the whole group (n=60). Values compared to baseline: * $p<0.01$. O significantly different from predicted values, $p<0.05$.

In Table 7-3 the scores are shown of the psychological parameters before and after the training period and after one year. There were no differences between the baseline values in the three groups. In all groups baseline scores on anxiety, depression, physical complaints and social inadequacy were significantly higher than the predicted normal values. After the training period scores on anxiety and depression decreased significantly in the PR group and the PR+IMT group. After the follow-up period these scores were still significantly decreased in the PR group, but not in the PR+IMT group. In the IMT group there were no changes in these parameters. There were no significant differences between the changes in the three groups.

	W_{max}	12-MWD	ADL
Anxiety	-.10	-.22	-.34*
Depression	-.12	-.26*	-.46***
Hostility	.10	-.12	-.33**
Physical complaints	-.02	-.29*	-.48***
Social inadequacy	-.13	-.24	-.28*
Self-esteem	-.12	.10	.22
TLC (%pred)	.27*	.26*	.16
IVC (%pred)	.35**	.29*	.24
FEV_1 (%pred)	.47***	.41***	.16

Table 7-4. Correlation coefficients of baseline psychological and lung function parameters versus baseline values of maximal work load (W_{max}), twelve-minute walking distance (12-MWD) and Activities-in-Daily-Life (ADL) scores in all (sixty) patients. * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

The correlations of baseline psychological and lung function parameters versus baseline values of W_{max}, twelve-minute walking distance and ADL scores in the patients are presented in Table 7-4. The psychological parameters were significantly correlated to ADL scores, but not to tests of the exercise capacity (except for scores on depression and physical complaints which were correlated to the walking distance). Lung function parameters were significantly related to tests of the exercise capacity, but not to ADL scores.

Table 7-5 shows the correlations between baseline psychological parameters and changes of the exercise capacity during the study period. There was no uniform pattern in these correlations.

The correlations between changes of psychological parameters and changes of the exercise capacity are shown in Table 7-6. Again, no clear correlation between these changes could be detected. Thus, although scores on anxiety and depression, as well as ADL scores were significantly improved after the training period, these changes were not uniformly correlated to each other.

	▲ W_{max}			▲ 12-MWD			▲ ADL		
	PR	PR+IMT	IMT	PR	PR+IMT	IMT	PR	PR+IMT	IMT
Anxiety									
10 weeks	.24	-.50*	.22	.29	.26	-.19	.68**	-.01	.22
1 year	.07	-.06	.37	.06	.39	.10	.24	-.09	.01
Depression									
10 weeks	.18	-.57**	.43	.28	.24	-.29	.74***	.13	.26
1 year	.20	-.03	.54*	.12	.51*	-.03	.23	-.01	.01
Hostility									
10 weeks	-.17	-.50*	.45*	.39	.03	-.06	.41	.21	.39
1 year	-.25	-.32	.57*	.46	.17	-.12	.42	.23	-.51*
Physical complaints									
10 weeks	-.08	-.67**	.48*	.50*	.36	-.25	.50*	.03	.14
1 year	.18	-.23	.45	.36	.50*	.15	.24	-.03	.01
Social inadequacy									
10 weeks	.03	-.42	-.14	.27	.38	-.28	.52*	.01	.29
1 year	.07	-.36	.01	-.13	.30	.34	.08	.01	-.31
Self-esteem									
10 weeks	-.08	.49*	-.05	-.23	-.31	-.15	-.31	-.11	-.01
1 year	-.11	.20	-.15	-.02	-.42	-.19	.02	-.08	-.15

Table 7-5. Correlation coefficients between **baseline** psychological parameters and **changes** (values after minus before) in the maximal work load (▲ W_{max}), 12-min. walking distance (▲ 12-MWD) and Activities-in-Daily-Life scores (▲ ADL) after the ten-week training period and after a one year follow-up.

7-4. DISCUSSION

Pulmonary rehabilitation alone or in combination with inspiratory muscle training had a beneficial effect on the exercise capacity and on several psychological parameters in COPD patients with a ventilatory limitation during exercise.
The COPD patients at the start of this study showed significantly increased scores on anxiety, depression and physical complaints compared to the reference values for this group of patients. This

	▲ W_{max}			▲ 12-MWD			▲ ADL		
	PR	PR+IMT	IMT	PR	PR+IMT	IMT	PR	PR+IMT	IMT
▲ Anxiety									
10 weeks	-.13	-.09	-.09	-.52*	.22	-.34	-.63**	.13	.05
1 year	.17	.13	.12	.05	.02	.09	-.22	-.19	-.17
▲ Depression									
10 weeks	-.07	.07	-.40	-.32	-.08	-.05	-.68**	-.39	.03
1 year	.09	.20	-.35	-.07	-.11	.33	-.12	-.31	-.01
▲ Hostility									
10 weeks	.40	.21	-.43	-.46*	-.10	-.10	.24	-.16	-.40
1 year	.48	.10	-.41	-.60*	-.52*	.23	-.52*	-.24	.01
▲ Phys. complaints									
10 weeks	-.10	.02	-.10	-.42	-.22	.14	-.42	.05	.08
1 year	-.09	.07	.14	-.36	-.20	.22	-.18	-.64**	.03
▲ Social inadequacy									
10 weeks	.02	-.20	.15	-.09	-.26	.23	-.40	.42	.28
1 year	.43	.06	-.01	-.04	.08	.10	-.21	.48	.39
▲ Self-esteem									
10 weeks	.26	-.09	-.11	-.32	-.09	.08	-.01	-.08	.31
1 year	.38	.03	-.47*	-.01	-.02	.22	.07	.06	.24

Table 7-6. Correlation coefficients between **changes** (values after minus before) in psychological parameters and the **changes** in maximal work load (▲ W_{max}), twelve-minute walking distance (▲ 12-MWD) and Activities-in-Daily-Life scores (▲ ADL) after ten weeks and after one year.

is consistent with the results reported in other studies on COPD patients (9-12).

PR with or without additional TF-IMT resulted in a decrease of anxiety and depression, but there were no significant differences between the two patient groups. TF-IMT alone had no effects on the psychological parameters. This suggests that the improvement of these parameters is solely due to PR. Levine (12) showed a significant improvement of psychological parameters after ventilatory muscle endurance training, compared to baseline values. This improvement, however, was not different from the psychological changes in a "placebo" group performing intermittent positive pressure breathing. Therefore, training of only the inspiratory muscles is not likely to have effects on psychological parameters.

Lung function parameters were correlated to the maximal working capacity and the twelve-minute walking distance. These relationships are known from other studies (11,13,14). The best correlation was demonstrated for the FEV_1. With this value one can predict the exercise capacity for a group of patients to some extent. The correlation is too weak, however, to estimate the exercise capacity in the individual patient.

The patient's performance in daily life showed no correlation to lung function parameters, but much more to psychological characteristics. This also confirms the results of other studies (15,16).

The model of the vicious circle, as described in the introduction, predicts that physical performance and the psychological status influence each other. Improvements in one of these two aspects would break the vicious circle and would consequently lead to improvement of the other. The physical performance and the psychological status were indeed improved in this study, but independently of each other. This means that both aspects are not simply linked in a proportional way. Apparently, other factors, either inside or outside this vicious circle, make these relationships more complex. One of these factors may be the sensation of dyspnea. Other factors may be personality traits and social support.

Another explanation may be that there are several unrelated mechanisms by which the psychological parameters and the physical performance improve during a PR program. Patient education, for example, may have effects on symptoms like anxiety and depression, whereas exercise training influences the maximal exercise capacity. Furthermore, it might be possible that the tools (questionnaires) used to quantify the psychological status are not adequate or not sensitive enough. More investigations in

this field are certainly needed.
After the one-year follow-up period anxiety and depression were still improved in the PR group, but not in the PR+IMT group. This may be a result of the different baseline scores on these items between the two groups, although these differences were not statistically significant. The reduction of the ADL scores after one year indicates the need of continuation of physical activities after the training period.
It is concluded that psychological parameters and the exercise capacity are improved independently of each other during pulmonary rehabilitation. Physical exercise training and patient education contribute to these improvements and are important parts of a pulmonary rehabilitation program.

7-5. SUMMARY

The effects of pulmonary rehabilitation (PR), target-flow inspiratory muscle training (IMT) and a combination of both treatments (PR+IMT) on psychological parameters and the physical performance were studied in a group of sixty COPD patients with a ventilatory limitation during exercise (mean age ±59, mean FEV_1 ±50 per cent of predicted). After a ten-week training period scores of anxiety and depression were decreased in the PR and the PR+IMT group, but not in the IMT group. In the PR group these scores were still decreased after a one-year follow-up period. Maximal work load and the activities-in-daily-life (ADL) scores were improved significantly after the training period in the PR and the PR+IMT group. Most of these improvements had disappeared after one year. The twelve-minute walking distance was increased in all patient groups after the training period and was still increased after the follow-up period.
The exercise capacity was correlated significantly to lung function parameters. ADL scores, however, were not correlated with lung function parameters, but were closely related to psychological parameters. The improvement of the psychological parameters was not correlated to the improvement of the exercise

capacity after the training period or after one year.

The results indicate that psychological parameters and physical condition are improved by different mechanisms during a pulmonary rehabilitation program.

7-6. REFERENCES

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CHAPTER 8

SUMMARY AND CONCLUSIONS

Chapter 1 presents a general introduction and an outline of the objectives of the studies reported in this thesis.
In patients with chronic obstructive pulmonary disease (COPD) the physical exercise capacity is usually diminished. In COPD patients with a ventilatory limitation during exercise, weakness and fatigability of the inspiratory muscles may contribute to the limitation of the exercise capacity. Since CO_2-transport is ventilatorily limited, a ventilatory exercise limitation will express itself by an increase in the arterial PCO_2 during incremental exercise.
In previous studies physical exercises as well as specific inspiratory muscle training were used in patients with COPD. The effects of inspiratory muscle training on the performance of the inspiratory muscles and the exercise capacity are controversial. There are several reasons for this controversy. Most studies did not select COPD patients on the basis of an insufficiency of the inspiratory muscles which contributed to the exercise limitation. Also, in most of the studies it is doubtful whether an adequate training stimulus was given to the inspiratory muscles. Furthermore, the long-term effects were not studied.
The aims of the investigations presented in this thesis are to study the acute and long-term effects of pulmonary rehabilitation and inspiratory muscle training on the performance of the inspiratory muscles, the physical exercise capacity and psychological parameters in COPD patients with a ventilatory limitation of their exercise capacity.

In **Chapter 2** the mechanisms of limitations of the physical exercise capacity in COPD patients are discussed.
In patients with mild COPD the cardiocirculatory system may limit the exercise capacity. These patients will reach their predicted maximal heart rate during exercise. In more severe COPD a reduced diffusion capacity may be responsible for the decreased exercise capacity, which will become clear by the lowering of the arterial PO_2 during exercise.

A ventilatory limitation is caused by the reduced ventilatory capacity and the increased work of breathing. The inspiratory muscles have to perform this increased work load. These muscles, however, can be weak in COPD. Moreover, hyperinflation influences the function of the diaphragm negatively by placing it on the unfavourable part of its length-tension curve. These factors result in an increased fatigability and can lead to failure of the inspiratory muscles to maintain an adequate alveolar ventilation. This occurs especially in conditions in which the work load is increased, as during exercise for example. Disorders in the mechanics of breathing are often associated with a ventilatory limitation.
Pulmonary rehabilitation may result in an increased work capacity, which can be caused by increased skills, a better performance of the inspiratory muscles and sometimes by an increase of the aerobic power. Specific inspiratory muscle training may result in an increase in strength and endurance of these muscles. The effects on the general exercise capacity are not clear. Factors that may contribute to these controversies are the above-mentioned non-specified patient selection and a poorly defined and possibly inadequate method of inspiratory muscle training in most reported studies.

Chapter 3 presents the study of the acute effects of target-flow inspiratory muscle training (TF-IMT) on the breathing pattern and the effects of this additional inspiratory load on the metabolic demands in a group of twelve COPD patients with a ventilatory limitation of their exercise capacity and in fifteen normal subjects. TF-IMT was performed by means of an incentive flowmeter with an added resistance. This permits control of the generated inspiratory airflow and the generated inspiratory mouth pressure, which had to be 70 per cent of PI_{max}. The duration of the inspiration was three seconds and of the (unloaded) expiration four seconds. In the COPD group minute ventilation ($\dot{V}E$), ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) and dead space to tidal volume ratio (VD/VT) decreased significantly during a session of TF-IMT. These changes persisted during a recovery

period of five minutes after stopping TF-IMT. In the control group $\dot{V}E/\dot{V}O_2$ and VD/VT also decreased during TF-IMT, but $\dot{V}E$ did not change. During the recovery phase $\dot{V}E/\dot{V}O_2$ and VD/VT returned to baseline values. The arterial pCO_2, oxygen uptake and blood lactate did not change in both groups during the training session. In the COPD patients a ten-week training period of TF-IMT for fifteen minutes, twice a day resulted in a significant increase in the maximal inspiratory mouth pressure.
These results indicate that TF-IMT gave an adequate training stimulus to the inspiratory muscles in these patients without causing hypoventilation during the training.

In **Chapter 4** the effects of additional TF-IMT during pulmonary rehabilitation (PR) were investigated. Forty COPD patients with a ventilatory limitation of the exercise capacity were randomised to receive either additional TF-IMT (PR+IMT group, n=20) or not during a ten-week PR program (PR group, n=20). This PR program consisted of exercise training, callisthenics, conventional physiotherapy and education about the pulmonary disease and the medications. TF-IMT was performed for fifteen minutes, twice a day during ten weeks. The mean age of the patients was 59, the mean FEV_1 was approximately 50 per cent of predicted.
After the training period inspiratory muscle strength (PI_{max}) and the endurance of the diaphragm (as measured by the EMG-fatigability during static inspiratory manouvres) had improved in both groups, but the improvement was significantly greater in the PR+IMT group than in the PR group (Table 8-1).
Maximal work load, maximal ventilation, maximal oxygen consumption and activities-in-daily-life (ADL) scores increased to the same extent in both groups (Table 8-1).
The twelve-minute walking distance also increased in both groups, but there was a significantly greater increase in the PR+IMT group than in the PR group.

	baseline	10 weeks	1 year
PI_{max}, kPa			
PR	5.3	6.9 **	6.6 *
PR+IMT	5.4	8.0 **O	7.5 **
IMT	5.9	7.9 **O	7.3 **
$tgF_{C}DIA$, Hz/sec			
PR	-.07	-.04 **	-.08
PR+IMT	-.08	-.01 **O	-.05
IMT	-.07	-.04	-.06
Walking distance, m			
PR	1057	1251 **#	1222 **
PR+IMT	1046	1309 **##O	1262 **
IMT	1065	1207 **	1191 *
ADL scores			
PR	6.3	7.7 **##	7.4
PR+IMT	6.2	8.4 **##	7.0
IMT	6.4	6.3	6.3

Table 8-1. Inspiratory muscle strength (PI_{max}), electromyographic fatigability of the diaphragm ($tgF_{C}DIA$), twelve-minute walking distance and Activities-in-Daily-Life (ADL) scores before and after the ten-week training period and after a one-year follow-up in the three groups. PR: Pulmonary rehabilitation; IMT: Inspiratory muscle training. Values are means. Data compared to baseline: * $p<0.05$; ** $p<0.01$. Data compared to PR: O $p<0.05$. Data compared to IMT: # $p<0.05$, ## $p<0.001$.

In **Chapter 5** the effects of a ten-week TF-IMT program at home were compared to TF-IMT during a PR program in two groups of twenty COPD patients with a ventilatory limitation of the exercise capacity. Patients who were unable to visit the outpatient clinic daily because of geographic or transport problems, performed TF-IMT at home. In the training period inspiratory muscle strength improved in both groups to the same degree. EMG-fatigability of the diaphragm improved in the PR+IMT group, but not in the IMT group (Table 8-1). In the IMT group, the twelve-minute walking distance increased after the training period, but maximal work load, maximal ventilation, maximal oxygen consumption and ADL scores did not change. In the PR+IMT group, however, maximal work load, maximal ventilation, maximal oxygen consumption and ADL scores improved significantly after the training period. Walking distance and ADL scores showed a significantly greater improvement in the PR+IMT group than in the IMT group.

In **Chapter 6** the long-term effects of TF-IMT and PR are described in the three patient groups (isolated PR, PR combined with TF-IMT and TF-IMT alone). Inspiratory muscle strength and the twelve-minute walking distance improved in all groups during the ten-week training period and remained above the baseline values at three, six and twelve months after the training period (Table 8-1). The initial improvement of the EMG-fatigability of the diaphragm in the PR and the PR+IMT group after the training period disappeared during the follow-up period (Table 8-1). Maximal work load and ADL scores were increased significantly in the PR and the PR+IMT group during the training period, but these improvements had disappeared after one year, except for the maximal work load in the PR group.

In **Chapter 7** the effects of the training programs on psychological parameters in the three patient groups are presented. Comparing the scores to normal values, the patients scored high on anxiety, depression and physical complaints and low on self-esteem. The scores on anxiety and depression decreased significantly after the PR program and after PR combined with TF-IMT. One year after the training period these scores remained below the baseline scores in the PR group, but not in the PR+IMT group. Isolated IMT at home had no acute or long-term effects on these scores.
Lung function parameters were significantly correlated to the maximal work load and the twelve-minute walking distance. ADL scores, however, were not correlated with lung function parameters, but were closely related to psychological parameters.

The improvement of the psychological parameters was not correlated to the improvement of the exercise capacity after the training period or after one year. These results indicate that a pulmonary rehabilitation program improves psychological parameters and the physical condition via different unrelated mechanisms, like patient education and exercise training.

CONCLUSIONS

1. In COPD patients with a ventilatory limitation during exercise, weakness and fatigability of the inspiratory muscles contribute to the decreased physical exercise capacity. These patients benefit from inspiratory muscle training.

2. During inspiratory muscle training, an adequate training stimulus to the inspiratory muscles is only given when a target-flow or target-pressure is defined as well as the duration of inspiration and expiration. Visual feedback on these parameters as well as regular supervision are essential for optimal inspiratory muscle training.

3. Pulmonary rehabilitation results in a substantial increase in strength and endurance of the inspiratory muscles and in an improved exercise capacity of COPD patients with a ventilatory limitation during exercise. Additional target-flow inspiratory muscle training has significant additional effects on the performance of the inspiratory muscles and on the 12-minute walking distance compared to pulmonary rehabilitation alone.

4. Isolated target-flow inspiratory muscle training at home increases inspiratory muscle strength and the twelve-minute walking distance, but has no effects on the electromyographic fatigability of the diaphragm, maximal work load, activities in daily life or psychological parameters. Isolated target-flow inspiratory muscle training should therefore not be recommended.

5. The acute effects of pulmonary rehabilitation and target-flow inspiratory muscle training on the maximal work load and activities in daily life are lost after a one-year follow-up period. This stresses the need of continued physical exercises after the training period.

6. Psychological parameters are favourably influenced during pulmonary rehabilitation with or without additional target-flow inspiratory muscle training. Psychological parameters and the exercise capacity may improve independently of each other. Therefore, the rate of improvement of the exercise capacity during these training programs cannot be predicted by psychological factors.

SAMENVATTING

De inspanningscapaciteit van patiënten met een chronisch obstructief longlijden (COPD) is in het algemeen verlaagd. Een ventilatoire stoornis tijdens inspanning kan één van de oorzaken zijn. Dit komt tot uiting in een stijging van de arteriële PCO_2 ten opzichte van de uitgangswaarde. De chronische luchtwegobstructie en het dysfunctioneren van de inademingsspieren zijn de belangrijkste factoren bij het ontstaan van een ventilatoire stoornis.

Hoofdstuk 1 bevat een algemene introductie en een toelichting op de verschillende onderzoekingen.
Algemene lichamelijke training en specifieke training van de inademingsspieren zijn toegepast bij patiënten met COPD. De effecten hiervan op de inspanningscapaciteit en op het functioneren van de inademingsspieren zijn tegenstrijdig. Hiervoor zijn verschillende verklaringen mogelijk. In de meeste studies is geen onderscheid gemaakt tussen COPD patiënten bij wie het dysfunctioneren van de inademingsspieren wel of niet een rol speelt bij de afname van de inspanningscapaciteit. Daarnaast is het twijfelachtig of de methode van training van de inademingsspieren in alle studies resulteerde in een adequate trainingsprikkel voor deze spieren. Bovendien zijn de meeste studies van korte duur en zijn de lange-termijn effecten nog onbekend.
Het doel van deze studie is na te gaan welke korte-, en lange-termijn effecten een longrevalidatie programma en specifieke training van de inademingsspieren bij patiënten met een aangetoonde ventilatoire beperking tijdens inspanning hebben op het functioneren van de inademingsspieren, op de algemene inspanningscapaciteit en op het psychologisch welbevinden.

In **hoofdstuk 2** worden de verschillende oorzaken van de afname van de inspanningscapaciteit bij patiënten met COPD toegelicht.
Patiënten met een lichte luchtwegobstructie worden, evenals normale personen, in hun prestatievermogen beperkt door het

cardiocirculatoire systeem. Bij maximale inspanning zullen deze patiënten hun voorspelde maximale hartfrequentie bereiken.

Bij patiënten met een ernstige chronische obstructieve luchtwegaandoening en emfyseem is de afname van de diffusiecapaciteit de beperkende factor. In dat geval treedt een daling van de arteriële PO_2 op tijdens inspanning.

Een ventilatoire beperking van de inspanningscapaciteit treedt vooral op bij patiënten met een matig ernstige luchtwegobstructie, waarbij de FEV_1 beperkt is tot 50 à 60 procent van de voorspelde waarde. Verschillende factoren spelen een rol bij het ontstaan van een ventilatoire beperking. Enerzijds is de ventilatoire capaciteit van het respiratoire systeem afgenomen ten gevolge van de luchtwegobstructie. Daarbij is de ademarbeid toegenomen. Anderzijds is de ademefficientie verminderd, met name door de verhoogde dode ruimte ventilatie en de ventilatie-perfusie ongelijkmatigheid. Deze ademarbeid wordt geleverd door de inademingsspieren. Het functioneren van de inademingsspieren bij COPD patiënten wordt echter vaak bemoeilijkt door zwakte van deze spieren. Bovendien is de rustlengte van het diafragma op FRC niveau afgenomen ten gevolge van de hyperinflatie. Het diafragma opereert daardoor op een ongunstig deel van het kracht-lengte diagram. Dit betekent dat de druk-genererende capaciteit van de gezamenlijke inademingsspieren is afgenomen. Tijdens lichamelijke inspanning kan bij deze patiënten vermoeidheid en dysfunctioneren van de inademingsspieren optreden en resulteren in (relatieve) alveolaire hypoventilatie met het oplopen van de arteriële PCO_2.

Ademmechanische problemen, zoals het oplopen van inspiratoire en expiratoire pleuradrukken tijdens inspanning tot in de buurt van hun maximale waarden, treden vaak op samen met een ventilatoire beperking.

De inspanningscapaciteit van patiënten met COPD kan worden verbeterd door middel van een longrevalidatie programma. Deze verbetering kan worden veroorzaakt door een toegenomen efficiëntie, een verbeterde conditie van de inademingsspieren en soms een toename van het cardiocirculatoire zuurstof-transport.

De conditie van de inademingsspieren kan ook verbeterd worden door gerichte training van deze spieren. De effecten van deze

wijze van training op de algehele inspanningscapaciteit zijn echter controversiëel. Factoren die hierbij een rol spelen zijn, zoals reeds eerder werd opgemerkt, het ontbreken van een adequate selectie van patiënten en een mogelijk ineffectieve methode van inademingsspier-training.
Het is onbekend of het toevoegen van inademingsspier-training aan een longrevalidatie programma resulteert in een extra verbetering van de algemene conditie en/of de conditie van de inademingsspieren.

In **hoofdstuk** 3 worden de metabole veranderingen en de acute effecten van "target-flow" inademingsspier-training op het ademhalingspatroon beschreven.
Twaalf COPD patiënten met een ventilatoire beperking en vijftien normale controle-personen werden onderzocht. Target-flow inademingsspier-training werd verricht met behulp van een "incentive flowmeter" met een toegevoegde externe weerstand. De target-flow was op een dusdanige wijze ingesteld dat bij elke inspiratie 70 procent van de maximale inspiratoire monddruk gegenereerd moest worden. De duur van de inspiratie was drie seconden, van de (onbelaste) expiratie vier seconden.
In de COPD groep namen het adem-minuut volume ($\dot{V}E$), ventilatoir equivalent voor O_2 ($\dot{V}E/\dot{V}O_2$) en de dode-ruimte/teug-volume ratio (VD/VT) significant af tijdens vijftien minuten target-flow inademingsspier-training. Vijf minuten na het beëindigen hiervan bestonden deze veranderingen nog steeds. In de controle groep namen $\dot{V}E/\dot{V}O_2$ en VD/VT ook af tijdens target-flow inademingsspier-training, maar $\dot{V}E$ veranderde niet. Tijdens de herstelfase bereikten $\dot{V}E/\dot{V}O_2$ en VD/VT de uitgangswaarden. In beide groepen veranderden de arteriele PCO_2, de zuurstofopname en het lactaat niet tijdens vijftien minuten inademingsspier-training.
De COPD patiënten namen vervolgens deel aan een trainingsprogramma, bestaande uit target-flow inademingsspier-training twee maal daags vijftien minuten gedurende tien weken. Na deze periode was de inademingskracht (PI_{max}) toegenomen van (gem. (SD)) 5.7 (2.2) tot 8.2 (2.7) kPa.
Deze bevindingen geven aan dat target-flow inademingsspier-

training resulteert in een adequate trainingsprikkel voor de inademingsspieren. Deze trainingswijze werd goed verdragen door de patiënten.

Hoofdstuk 4 geeft de effecten weer van additionele target-flow inademingsspier-training gedurende een longrevalidatie programma. Veertig COPD patiënten met een ventilatoire beperking van hun inspanningscapaciteit namen deel aan het revalidatie programma. De patiënten werden willekeurig geplaatst in één van de twee groepen: een tien weken durend longrevalidatie programma (longrevalidatie groep, n=20) of hetzelfde programma gecombineerd met target-flow inademingsspier-training (longrevalidatie met inademingsspier-training, n=20). Dit longrevalidatie programma bestond uit inspanningstraining, behendigheidsoefeningen, conventionele fysiotherapie en voorlichting over de pulmonale afwijkingen en de medicatie.
Target-flow inademingsspier-training werd tien weken lang twee maal daags gedurende vijftien minuten verricht. Eén maal daags werd de training verricht onder supervisie van de fysiotherapeut.
De gemiddelde leeftijd van de patiënten was 59 jaar, de gemiddelde FEV_1 was omstreeks 50 procent van de voorspelde waarde.
Na de trainingsperiode waren de inademingsspier-kracht (PI_{max}) en de electromyografische (EMG-) vermoeibaarheid van het diafragma (tgF_CDIA) verbeterd in beide groepen, maar in de groep met additionele target-flow inademingsspier-training waren deze veranderingen significant groter dan in de groep zonder target-flow inademingsspier-training (tabel).
In beide groepen waren de maximale belastbaarheid op de fietsergometer, de maximale ventilatie, de maximale zuurstofopname en de dagelijkse activiteiten scores in gelijke mate toegenomen. De twaalf-minuten loopafstand was na de trainingsperiode toegenomen in de longrevalidatie groep en in de groep met longrevalidatie + inademingsspier-training. De toename in de groep met additionele target-flow inademingsspier-training was echter significant groter dan in de longrevalidatie groep (tabel).

	baseline	10 weken	1 jaar
PI_{max}, kPa			
LR	5.3	6.9 **	6.6 *
LR+IST	5.4	8.0 **O	7.5 **
IST	5.9	7.9 **O	7.3 **
$tgF_{C}DIA$, Hz/sec			
LR	-.07	-.04 **	-.08
LR+IST	-.08	-.01 **O	-.05
IST	-.07	-.04	-.06
12-min. loopafstand, m			
LR	1057	1251 **#	1222 **
LR+IST	1046	1309 **#O	1262 **
IST	1065	1207 **	1191 *
ADL scores			
PR	6.3	7.7 **##	7.4
PR+IST	6.2	8.4 **##	7.0
IST	6.4	6.3	6.3

Tabel. Inademingsspierkracht (PI_{max}), electromyografische vermoeibaarheid van het diafragma ($tgF_{C}DIA$), twaalf-minuten loopafstand en Activiteiten-in-Dagelijks-Leven (ADL) scores voor en na de trainingsperiode en na één jaar follow-up in de drie patiënten groepen. Hoe negatiever $tgF_{C}DIA$, des te groter is de vermoeibaarheid van het diafragma. LR: longrevalidatie; IST: inademingsspiertraining. De waarden zijn gemiddelden. Waarden vergeleken met de uitgangswaarden (baseline): * $p<0.05$; ** $p<0.01$. Waarden vergeleken met LR: O $p<0.05$. Waarden vergeleken met IST: # $p<0.05$, ## $p<0.001$.

Hoofdstuk 5 betreft een vergelijking van de resultaten van een target-flow inademingsspier-training programma in de thuissituatie (n=20) ten opzichte van target-flow inademingsspiertraining tijdens een longrevalidatie programma (n=20).
Twintig ventilatoir beperkte COPD patiënten die niet dagelijks de kliniek konden bezoeken vanwege geografische- of vervoersproblemen, namen deel aan het tien weken durende target-flow

inademingsspier-training programma in de thuissituatie.
De inademingsspierkracht (PI_{max}) nam in beide groepen in dezelfde mate toe (tabel). De EMG-vermoeibaarheid van het diafragma (tgF_cDIA) nam significant af in de longrevalidatie + inademingsspier-training groep, maar niet in de groep met alleen inademingsspier-training.
In deze groep met alleen inademingsspier-training nam de twaalf-minuten loopafstand toe na de trainingsperiode. De maximale belastbaarheid op de fietsergometer, maximale ventilatie en zuurstofopname, en dagelijkse activiteiten scores veranderden echter niet in de inademingsspier-training groep, maar namen wèl significant toe in de groep met het gecombineerde trainingsprogramma. De twaalf-minuten loopafstand en de dagelijkse activiteiten scores waren in de groep met beide trainingsvormen significant meer toegenomen dan in de groep met uitsluitend inademingsspier-training.

In **Hoofdstuk 6** worden de lange-termijn effecten van target-flow inademingsspier-training en longrevalidatie beschreven gedurende één jaar volgend op de trainingsperiode.
Tijdens de trainingsfase waren de patiënten gestimuleerd om verschillende lichamelijke activiteiten te continueren na de trainingsperiode. Desgewenst werd ook de inademingsspier-training voortgezet. Van de 60 patiënten die deelnamen aan de trainingsperiode, konden er tien niet vervolgd worden in het jaar na deze periode.
De kracht van de inademingsspieren (PI_{max}) en de twaalf-minuten loopafstand in de drie groepen (de longrevalidatie groep, de inademingsspier-training groep en de gecombineerde groep) bleven verhoogd ten opzichte van de uitgangswaarde (tabel). De aanvankelijke verbeteringen in de EMG-vermoeibaarheid van het diafragma en de dagelijkse activiteiten in de longrevalidatie en de longrevalidatie met inademingsspier-training groep namen af tijdens de follow-up periode. De initiële verbeteringen van het maximale prestatie vermogen waren na één jaar verdwenen in de longrevalidatie + inademingsspier-training groep, maar niet in de longrevalidatie groep.

Hoofdstuk 7 beschrijft de effecten van de drie trainingsprogramma's op psychologische parameters.

In de uitgangssituatie scoorden de patiënten hoog wat betreft angst, depressie en lichamelijke klachten, en laag met betrekking tot zelfwaardering, vergeleken met de referentiewaarden van gezonde personen.

Angst en depressie scores namen af na het revalidatieprogramma, al dan niet gecombineerd met target-flow inademingsspiertraining. Eén jaar na de trainingsperiode lagen deze scores in de longrevalidatie groep nog steeds onder de uitgangswaarden. In de groep met het gecombineerde trainingsprogramma waren deze scores echter weer teruggekeerd naar het niveau van de uitgangswaarden. Target-flow inademingsspier-training alléén had geen effect op de psychologische parameters.

Er was een significante correlatie tussen de longfunctie parameters aan de ene kant en zowel de maximale belastbaarheid op de fietsergometer als de twaalf-minuten loopafstand aan de andere kant. Psychologische parameters waren gecorreleerd met de dagelijkse activiteiten scores, maar niet met de longfunctie parameters. Er was géén correlatie tussen de verbetering van de psychologische parameters en de verbetering van de inspanningscapaciteit na de trainingsperiode of na één jaar.

Deze resultaten geven aan dat verschillende mechanismen binnen een longrevalidatie programma de verbetering van psychologische parameters en van de lichamelijke conditie bewerkstelligen. De interacties en verbanden tussen deze mechanismen zijn nog niet duidelijk. Zij zijn echter aanzienlijk complexer dan de simpele circulaire processen die in de literatuur zijn voorgesteld.

CONCLUSIES

1. In COPD patiënten **met een ventilatoire beperking** tijdens inspanning dragen zwakte en vermoeibaarheid van de inademingsspieren bij tot de afname van de inspanningscapaciteit. Deze patiënten hebben baat bij gerichte training van de inademingsspieren.

2. Training van de inademingsspieren resulteert alléén in een adequate trainingsprikkel, indien zowel een target-flow en/of target-pressure als de duur van de inspiratie en de expiratie zijn vastgesteld. Visuele controle op deze parameters en regelmatige supervisie zijn essentieel voor een optimale uitvoering van inademingsspier-training.

3. Een longrevalidatie programma resulteert in een substantiële verbetering van de kracht en de vermoeibaarheid van de inademingsspieren in **ventilatoir beperkte** COPD patiënten. Toegevoegde target-flow inademingsspier-training heeft significant gunstiger effecten op kracht en vermoeibaarheid van de inademingsspieren en op de twaalf-minuten loopafstand dan een longrevalidatie programma alleen.

4. Een thuis-programma bestaande uit target-flow inademingsspier-training leidt tot een verbetering van de kracht van de inademingsspieren en van de loopafstand. Dit programma heeft echter geen effecten op de electromyografische vermoeibaarheid van het diafragma, de maximale belastbaarheid op de fietsergometer, op activiteiten in het dagelijks leven, of op psychologische symptomen.
   Deze trainingswijze zonder een algemeen longrevalidatieprogramma dient derhalve niet aanbevolen te worden.

5. De acute effecten van een longrevalidatie programma en target-flow inademingsspier-training op de maximale belastbaarheid op de fietsergometer op activiteiten in het dagelijks leven zijn één jaar na de trainingsperiode verdwenen.
   Dit benadrukt de noodzaak van het continueren van lichamelijke oefeningen na de trainingsperiode.

6. Psychologische parameters zoals angst en depressie worden gunstig beinvloed tijdens een longrevalidatie programma met of zonder target-flow inademingsspier-training.
   Er is geen correlatie tussen deze verbetering en de verbetering van de inspanningscapaciteit. Psychologische parameters hebben geen voorspellende waarde ten aanzien van de mate van verbetering van de lichamelijke conditie tijdens deze trainingsprogramma's.

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CURRICULUM VITAE

De auteur van dit proefschrift werd op 13 januari 1956 geboren te Amsterdam. In 1974 behaalde hij het diploma gymnasium-ß aan het Vossius Gymnasium te Amsterdam. Vervolgens studeerde hij geneeskunde aan de Vrije Universiteit te Amsterdam. Na het behalen van het artsexamen (augustus 1981) begon hij met de vooropleiding Interne Geneeskunde in het Streekziekenhuis Gooi-Noord, Majella Ziekenhuis te Bussum (opleider: dr. D. Maingay). Vanaf 1 april 1984 was hij in opleiding tot longarts in het Onze Lieve Vrouwe Gasthuis te Amsterdam (opleider: dr. J.P.M. Wagenaar). In januari 1987 werd de opleiding voortgezet in het Universitair Longcentrum te Nijmegen (opleider: prof. dr. C.L.A. van Herwaarden). Op 1 april 1987 volgde inschrijving in het specialisten register. Sindsdien is hij verbonden als longarts aan het Universitair Longcentrum Nijmegen, bestaande uit de afdelingen longziekten van het Sint Radboud Ziekenhuis te Nijmegen en het Medisch Centrum Dekkerswald te Groesbeek.

STELLINGEN behorende bij het proefschrift

TARGET-FLOW INSPIRATORY MUSCLE TRAINING AND PULMONARY REHABILITATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

P.N.R. Dekhuijzen

1 Gerichte training van de inademingsspieren dient opgenomen te worden in een revalidatie programma voor ventilatoir beperkte CARA patiënten.

2 Specifieke training van de inademingsspieren als "monotherapie" heeft geringe effecten op de lichamelijke conditie en dient derhalve niet te worden toegepast.

3 Het bepalen van de maximale inspanningscapaciteit en het vaststellen van beperkende mechanismen is noodzakelijk om een optimaal longrevalidatie programma vast te stellen.

4 Gerichte training van de inademingsspieren is niet zinvol indien een ventilatoire beperking van de inspanningscapaciteit wordt vastgesteld tijdens een onvoldoende behandelde luchtwegobstructie.

5 Bij gerichte training van de inademingsspieren dienen de te genereren inspiratoire druk en het adempatroon te worden opgelegd.

6 Een gestructureerd nazorg-programma dient een essentieel onderdeel van een longrevalidatie programma te zijn.

7 Voor een juiste beoordeling van de arbeids(on)geschiktheid van long patiënten is een maximale inspanningstest met gelijktijdige registratie van het verloop van de inspiratoire en expiratoire pleurale drukken onontbeerlijk.

8 "Mede-opleiders" naast de opleider dienen een wezenlijke bijdrage te leveren aan de klinische specialisatie. De registratie als specialist en het in een (nagenoeg) volledige dagtaak werkzaam zijn, zoals vermeld in de opleidingseisen, bieden hiervoor onvoldoende garanties.

9 Met poep op de stoep is (Toxo-)CARA niet van de lucht.

10 Ook bij promovendi kan een stoornis in de inspiratie optreden. Het effect van reactivatie in deze situatie is nog onvoldoende onderzocht.